The Total Synthesis of Bryostatin 7

by

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Signature of Author _____
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To :

Mom and Dad, whose love and support has never faltered,

and

Carla, who has enriched my life in all ways imaginable.

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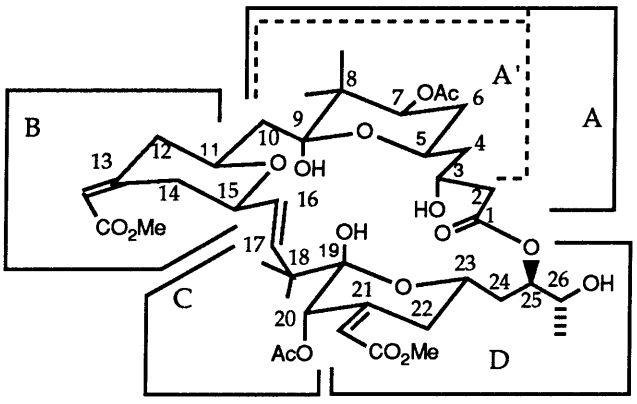
ABSTRACT

A collaborative study, ultimately leading to the first synthesis of bryostatin 7, is described. The first approach to this antineoplastic agent began with the synthesis of



Bryostatin 7

fragment A [C(1)-C(10)], fragment B [C(11)-C(16)], fragment C [C(17)-C(20)], and fragment D [C(21)-C(27)]. External chiral reagent-controlled aldol coupling of fragments A (ketone) and B (aldehyde) created the C(11)-stereogenic center and resulted in fragment AB [C(1)-C(16)].

Chelation-controlled addition of fragment D (carbon nucleophile) to fragment C (aldehyde) created the stereogenic center at C(20) and led to fragment CD [C(17)-C(27)]. Fragments AB (aldehyde) and CD (sulfone) were coupled by the Julia-Lithgoe olefination which produced the [C(16)-C(17)]-double bond. In this manner, the synthesis of a fully protected seco acid derivative of bryostatin 7 was completed, but unfortunately the protecting groups neither at O(3) (a methoxymethyl moiety) nor at the C(19)-hemiacetal (a methyl acetal moiety) could be hydrolyzed. The use of fragment A' [C(3)-C(10)] eventually led to a seco acid derivative minus the [C(1)-C(2)]-subunit, incorporated at this late stage of the synthesis utilizing external chiral reagent control. Macrolactonization of the resulting O(3)-unprotected seco acid was ultimately achieved under modified Keck conditions. Subsequently, the extremely stable C(19)-methyl acetal was rendered more labile by minor derivatization of the lower pyran ring, and the C(19)-deprotected product was converted to bryostatin 7.

Specific contributions of the author include : (i) a convergent synthesis of fragment A; (ii) synthesis of fragment B; (iii) a preparatively useful coupling of fragments A and B and elaboration to fragment AB; (iv) synthesis of a C(17)-thiophenyl fragment C; (v) use of the C(17)-thiophenyl C fragment in the C-D-coupling and elaboration to fragment CD; (vi) synthesis of fragment A'; (vii) coupling of fragments A' and B and elaboration to fragment A'B.

Thesis Supervisor: Satoru Masamune

Title: Professor of Chemistry

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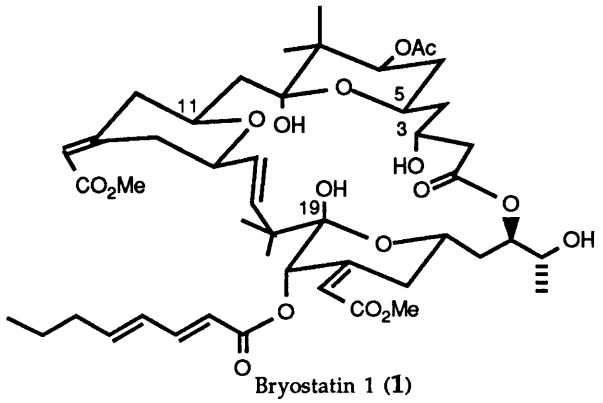
Chapter 1

Introduction to Bryostatins

1.1 Isolation, Structure, and Biological Activity of Bryostatins

The isolation, X-ray analysis, and potent biological activity of bryostatin 1 (**1**, Figure 1-1) was reported in 1982 by Pettit and co-workers.[1] Their first collection and

Figure 1-1



solvent extraction (in 1968) of the bryozoan, *Bugula Neritina*, a colonial filter-feeder often found attached to ship hulls, led to the finding that the crude extracts possessed marked anticancer properties.[2] After extensive work directed toward the isolation of the compounds responsible for this biological activity, it became clear that they existed in very small quantity. Ultimately, when the crude extracts from 500 kg of the organism (wet weight) were subjected to extensive chromatographic purification, a sufficient quantity of **1** was isolated for characterization (~300 mg).

With the relative stereostructure of **1** secured by X-ray crystallography, more detailed analysis of anomolous scattering effects due to oxygen and carbon indicated the absolute configuration shown above.[1] This assignment was recently confirmed.[3] Noteworthy is the hydrogen bonding between O(19)H and O(3) in the crystal structure and the possibility of such interactions between O(3)H and O(5), and O(3)H

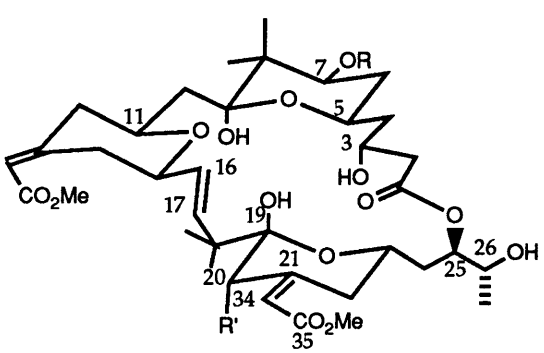
and O(11). The concentration dependent shifts in the ^1H NMR spectrum [particularly of the C(2)-methylene multiplet][4] suggest that considerable intermolecular interactions also exist.

Bryostatin 1 has a novel architecture. It contains a 26-membered macrolactone, three pyran rings, 11 stereogenic centers, two gem-dimethyl groups, and two exocyclic olefinic esters. It has been suggested that in its biosynthesis, as in that of aplasmomycin which contains some of the same structural features, acetate and methionine are precursors.[5]

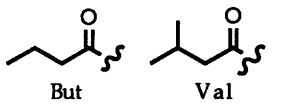
From 1982 to 1987 Pettit et al. reported the structure elucidation of **2** through **13** (Figure 1-2),*,[6] one of which (**8**) was first isolated from *Amantha Convoluta,*[6e] a bryozoan closely realated to *Bugula Neritina*. These structural assignments were based mostly on (i) spectral comparison with **1** and (ii) data generated from the use of an innovative technique of mass spectroscopy,[7] and could frequently be confirmed by converting the bryostatin being studied to a derivative that could also be prepared from **1**. The nine type I bryostatins (**1, 2, 4** to **9**, and **12**), differ only in their C(7)- and C(20)-ester moieties. The original structure assignment for **3**,[6b] the only type II compound known, could not be confirmed by chemical interconversions, and recently had to be revised based on X-ray analysis.[8] Oxygenation at C(22) and an [O(22)-C(35)]-lactone distinguish **3** from **1**. Finally there are the type III C(20)-desoxy bryostatins (**10, 11,** and **13**) which suffer from an extraordinary lability of their C(19)-hemiacetal which readily eliminates water to form the [C(19)-C(20)]-enol ether under mildly acidic conditions.[6g,6h] Yields of these 13 compounds range from 10^{-7} to 10^{-4} % (weight of isolated compound/weight of wet organism).

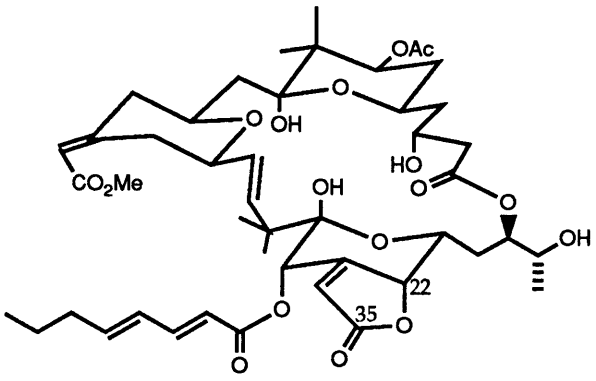
* For simplicity, bryostatins 1 through 13 are represented by the same numbers in **boldface** type.

Figure 1-2



	bryostatin	R	R'
type I	1	Ac	Oct-O
	2	H	Oct-O
	4	Val	But-O
	5	Val	Ac-O
	6	But	Ac-O
	7	Ac	Ac-O
	8	But	But-O
	9	Ac	But-O
	12	But	Oct-O
type III	10	Ac	H
	11	But	H
	13	But	H



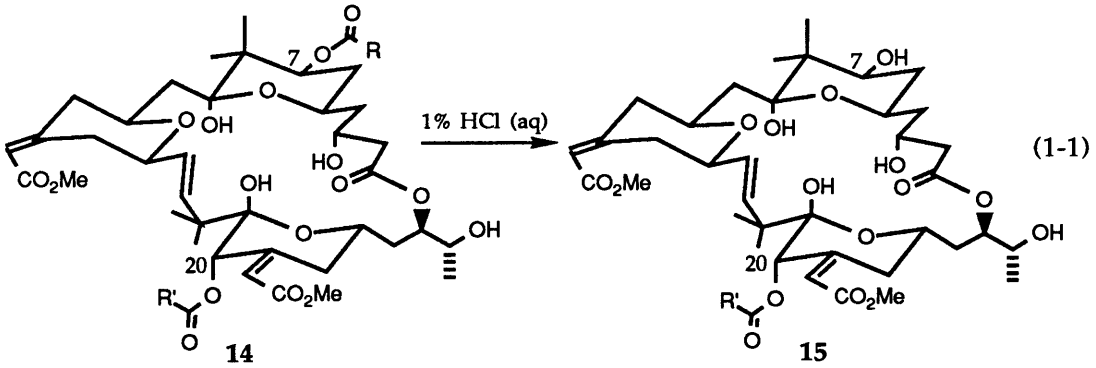


type II { bryostatin 3

The additional 12 bryostatins exhibit similar biological activity to **1** despite their variation in structure. In vivo studies of their effectiveness against and lymphocytic leukemia [with the U.S. National Cancer Institute's murine P388 lymphocytic leukemia (PS system)] exemplify their potent antineoplastic activity.[6,9] Extensive work on the biochemical behavior of bryostatins has also been completed despite the laborious nature of their isolation. Most notable are their immunomodulating properties[10] and their ability to stimulate normal bone marrow growth,[11] activate protein kinase C,[12] and bind to the phorbol receptor.[13]

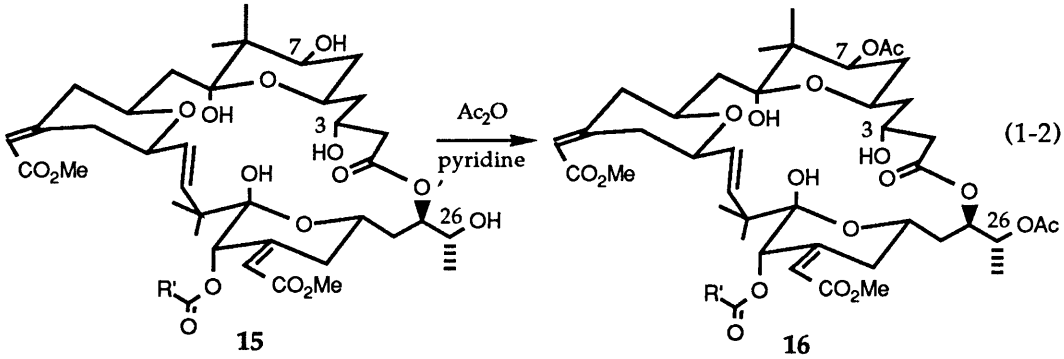
1.2 Reactivity of Type I Bryostatins

A number of research groups have selected type I bryostatins as synthetic targets.[14] When our synthesis began in 1984, some of the chemical properties of the type I bryostatins were known. Although sparse, this information aided us in initiating a synthetic design, particularly with respect to the last steps. It was known, for example, that some selectivity could be achieved in ester hydrolysis at C(7) over C(20) (**14** --> **15**, eq 1-1) under mildly acidic conditions [1% aqueous hydrochloric

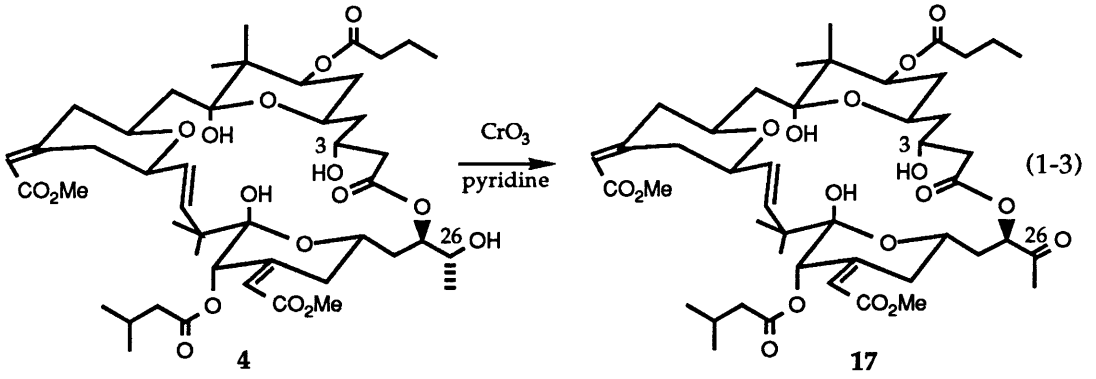


acid, room temperature, 25 h].[6c-f] Since 30-70% yields of the C(7)-alcohols were obtained, we inferred that distinction between the C(7)- and C(20)-oxygens would be straightforward.

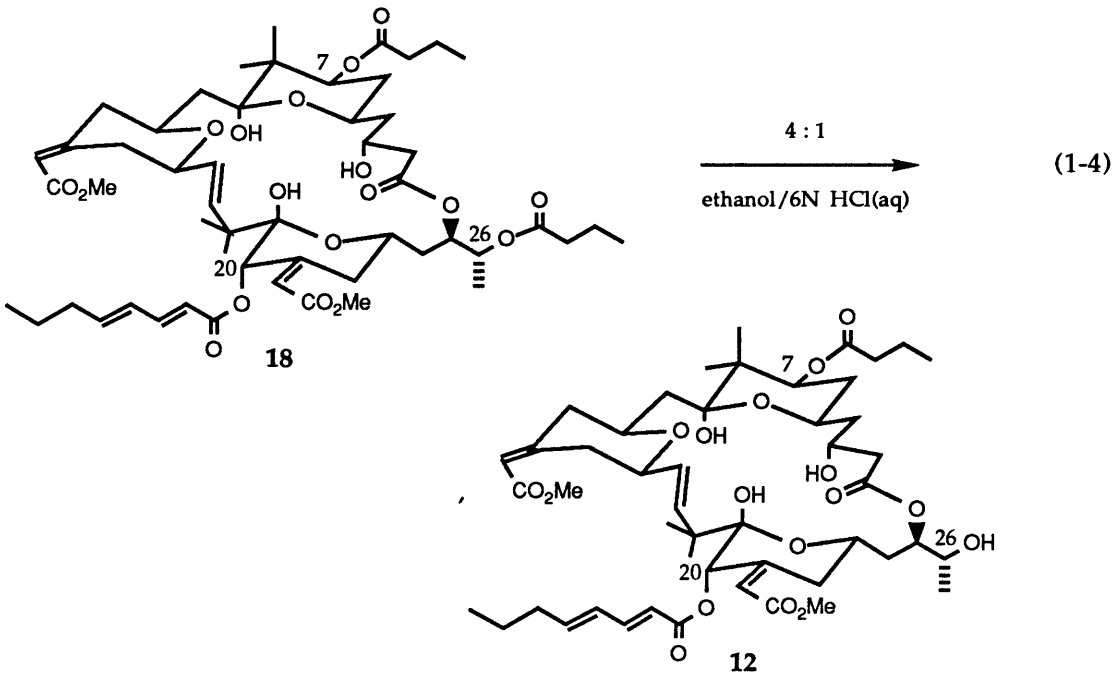
Esterification in pyridine (e.g. acetic anhydride, room temperature, 4 h) of the C(3)-, C(7)-, C(26)-triols had been described. These conditions provided only the C(7)-, C(26)-esters (e.g. **15** --> **16**, eq 1-2).[6d,6f] Presumably because of its location within the



macrolactone, the C(3)-alcohol moiety does not react under these conditions and it is also relatively inert to oxidation. For example, treatment of **4**, a C(3)-, C(26)-diol, with chromium trioxide in pyridine for 24 h at room temperature provided a 60% yield of the corresponding C(26)-ketone, the C(3)-hydroxyl moiety having survived the conditions admirably (**4** --> **17**, eq 1-3).[6g] Therefore, it was clear that the C(3)-hydroxyl group could be easily distinguished from those at C(7), C(20), and C(26).



Finally, in a non-selective acid hydrolysis (4:1 ethanol/aqueous 6N hydrochloric acid) (eq 1-4), Pettit et al. obtained a 20% yield of **12** from its C(26)-



butyrate (**18**).[6h] Note that the C(7)- and C(20)-ester moieties remained intact. The fact that one of the many hydrolysis products expected in this reaction could be isolated in such a respectable yield indicated to us that the type I bryostatin structure was relatively stable to acidic conditions.

Chapter 2

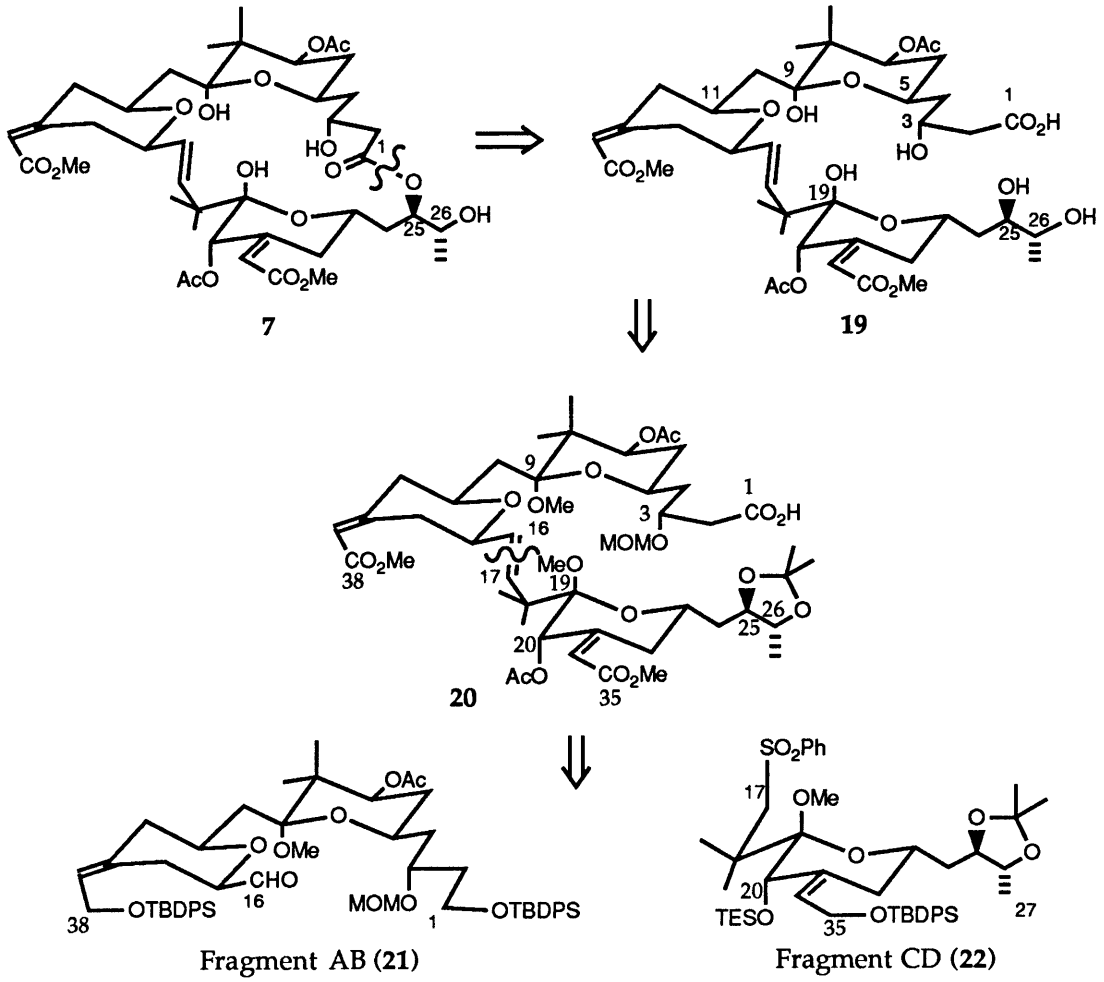
Planned Synthesis of Bryostatin 7

2.1 Retrosynthetic Analysis

Bryostatin **7**, a member of the type I group, was selected as our target molecule. A retrosynthetic scheme which involved macrolactonization[15] (rather than macrocyclic olefination[16]) appeared attractive. Close examination of the seco acid (**19**, Scheme 2-1) with CPK models revealed that although the transition states leading to both the C(25)- and C(26)-macrolactones would experience extensive steric congestion, the desired macrolactonization [involving the C(25)-hydroxyl group] was the less demanding of the two. Furthermore, if [O(3)H-O(5)]- and [O(3)H-O(11)]-hydrogen bonding played a decisive role in this intramolecular process, formation of the desired C(25)-lactone appeared to be unambiguously favored. Having made this optimistic, but obviously risky prediction (which we considered worth verifying), we planned to have the C(3)-, C(25)-, and C(26)-alcohol moieties free in the macrolactonization step. This plan greatly simplified the protecting group considerations for the rest of the retrosynthesis, an attribute that a macrocyclic olefination scheme did not offer. Thus, disconnection of **7** at the [O(25)-C(1)]-bond provided seco acid **19** (Scheme 2-1).

The relative acid stability of our synthetic targets (see section 1.2) invited us to utilize acid-labile protecting groups in our synthesis that could be removed in a step prior to lactonization. The C(9)- and C(19)-hemiacetals were envisaged as arising from their corresponding methyl acetals and the C(25)-, C(26)-diol from its corresponding acetonide. With respect to the C(3)-alcohol moiety, model studies indicated that β-hydroxy carboxylic acids, such as the [C(1)-C(3)]-subunit of **19**, could

Scheme 2-1



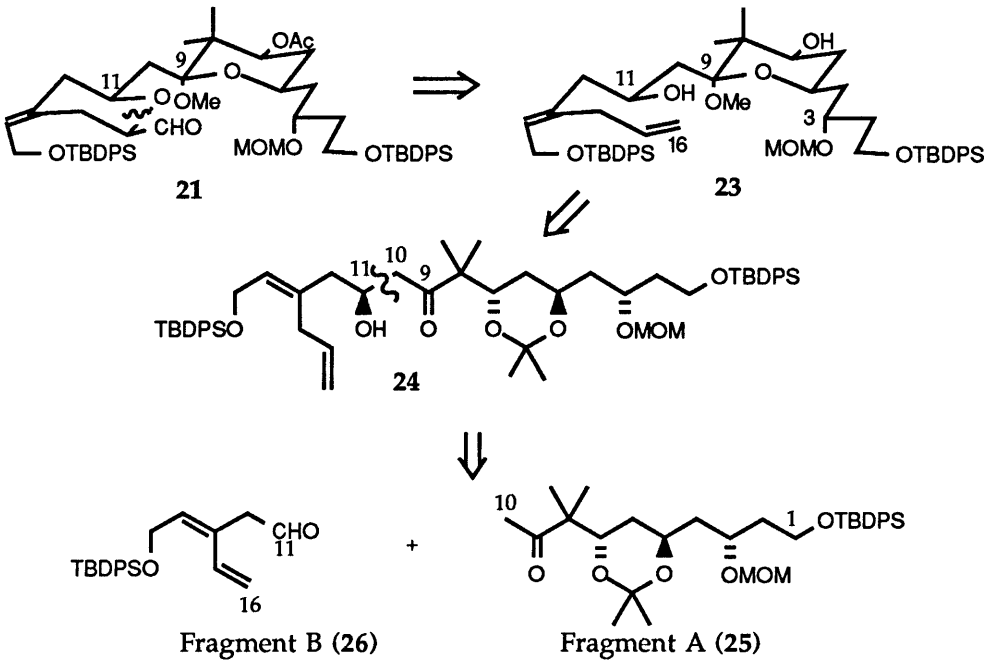
Fragment AB (21) Fragment CD (22)

be liberated from β-methoxymethyl, hydroxyl-protected carboxylic acids (see Chapter 6). Thus, fully protected seco acid derivative **20** was chosen as a potential precursor to seco acid **19**. The methyl ester moieties at C(35) and C(38) appeared most easily obtainable from the corresponding allylic alcohols via oxidation with manganese dioxide.[17] A C(1)-alcohol, predictably inert to this reagent, seemed an appropriate precursor to the carboxylic acid, and its inherent distinction from the allylic alcohols allowed us to select the *tert*-butyldiphenylsilyl (TBDPS) protecting group[18] for all three hydroxyl moieties. For differentiation at C(20), the more labile triethylsilyl (TES) protecting group[19] was chosen. At this stage, it was apparent that further

disconnection could be made at the [C(16)-C(17)]-olefin to secure the smaller fragments AB [**21**, C(1)-C(16)] and CD [**22**, C(17)-C(27)]. In the forward direction, a Julia-Lithgoe *E*-olefination[20] was considered appropriate for the union of these two fragments.

Examination of fragment AB (**21**) revealed a 1,3-relationship between a ketone equivalent [at C(9)] and an oxygenated stereogenic center [at C(11)], suggesting the applicability of aldol methodology (Scheme 2-2).[21] To exploit this relationship,

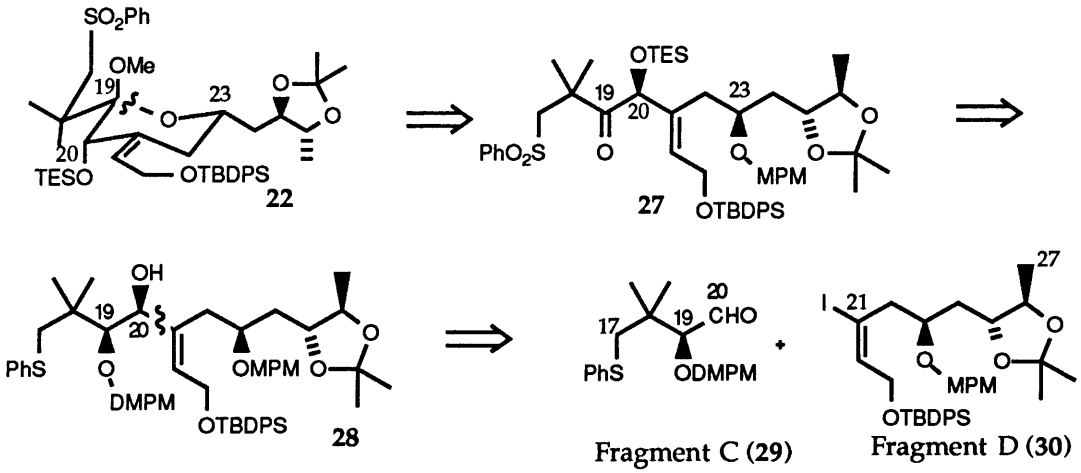
Scheme 2-2



21 was disconnected to β-hydroxy ketone **24**, via a retro mercuric cyclization[22] involving the [O(11)-C(15)]-bond to provide **23**, and opening of the remaining pyran ring. Disconnection at the [C(10)-C(11)]-bond led to fragments A [**25**, C(1)-C(10)] and B [**26**, C(11)-C(16)].

Fragment CD (**22**) was unraveled to the corresponding acyclic, C(23)-protected, ketone **27** (Scheme 2-3) in a plan that exploited the selective, oxidative removal of

Scheme 2-3



methoxy-substituted benzyl ethers (the MPM-O and DMPM-O moieties).*,[23] Alcohol **28**, the C(19)-reduced counterpart of **27**, was viewed as a more workable target which could be disconnected at the [C(20)-C(21)]-bond to afford fragment C [**29**, C(17)-C(20)] and fragment D [**30**, C(21)-C(27)]. In the forward direction, the stereogenic center at C(19) in **29** was envisaged as controlling the stereochemistry created at C(20) in the C-D-coupling.[24] It is appropriate to point out that the final choice of protecting groups for the C(19)- and C(23)-alcohols presented here was not obvious at the onset of the bryostatin project since the former would play a crucial (and unpredictable) role in the fragment-coupling step. It should also be noted that the absolute configuration of **29** [i.e. C(19)*S* or C(19)*R*] was only meaningful with respect to its effect on stereoselectivity at C(20) since the C(19)-center would later be oxidized to the ketone (as in **27**).

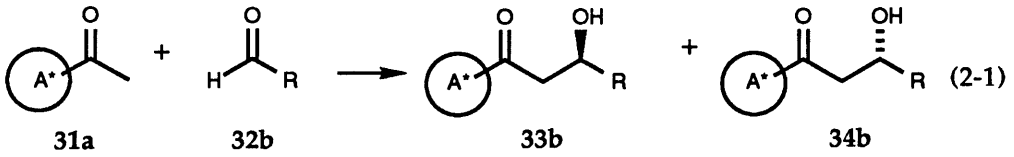
Of particular interest in our synthetic design was the intended fragment-coupling steps, each with concomitant creation of a stereogenic center [at C(11) and C(20)]. Indeed, the creation of the C(11)-stereogenic center (in the coupling of

* The 4-methoxybenzyl and 3,4-dimethoxybenzyl groups are designated as MPM and DMPM respectively.

fragments A and B) is an advanced application of double asymmetric synthesis (D.A.S.).[25]

2.2 Background on Double Asymmetric Synthesis (D.A.S.)

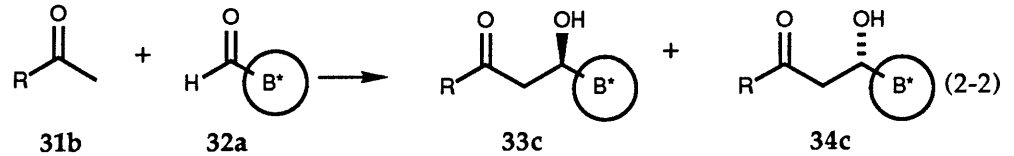
In a process of D.A.S., two chiral compounds with their own inherent diastereofacial selectivities (D.S.'s)* undergo a reaction in which at least one new stereogenic center is created. Intuition suggests that the resulting diastereomeric mixture should reflect the synergistic or antagonistic nature of these selectivities. Consider, for example, the reaction of chiral ketone **31a** with achiral aldehyde **32b** (a single asymmetric reaction) to provide a mixture of diastereomers in a ratio of a/b (eq 2-1). The D.S. of **31a** in this reaction (denoted here as DS_{A^*}) is thus a/b or b/a



31a **32b** **33b** **34b**

a : b

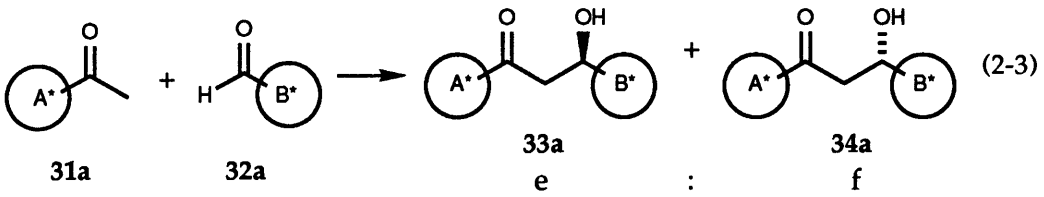
(always expressed as greater than unity). The single asymmetric reaction of achiral ketone **31b** with chiral aldehyde **32a** similarly allows for the definition of DS_{B^*} as c/d or d/c (eq 2-2). With respect to D.A.S., the diastereomeric ratio resulting from the reaction between chiral **31a** and chiral **32a** (eq 2-3) can be predicted from a knowledge



31b **32a** **33c** **34c**

, c : d

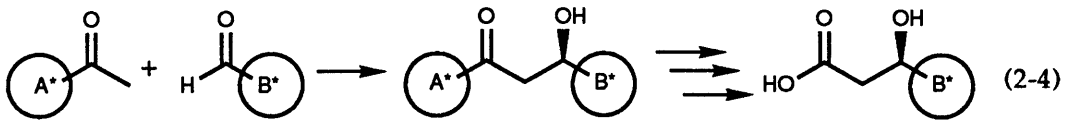
* The D.S. of a chiral reactant is defined as the ratio of diastereomers that are produced in its reaction with an achiral reactant and is expressed as ≥ 1. See Ref. 25.



of DS_{A^*} and DS_{B^*}. Indeed, from an analysis of the transition states of any double asymmetric reaction, a general rule can be derived as follows : *in the reaction of two chiral components, the ratio of diastereomers obtained is either the product (matched case) or the quotient (mismatched case) of the D.S.'s inherent to both components.*[25] Thus, returning the discussion to equation 2-3, we can predict that $e/f \sim (DS_{A^*})x(DS_{B^*})$ or $(DS_{A^*})/(DS_{B^*})$, depending on whether **31a** and **32a** react synergistically or antagonistically respectively. Conformational change in the transition state of a double asymmetric reaction (e.g. eq 2-3) relative to the transition states of the model single asymmetric reactions (e.g. eq 2-1 and 2-2) is usually small. Thus, empirical confirmation of the rule of D.A.S has been overwhelming.[26]

2.3 Background on Reagent-Controlled Asymmetric Synthesis

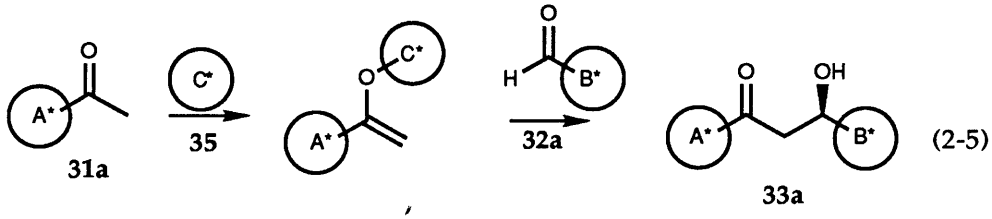
The rule of D.A.S ensures that if a reagent with a very high D.S. (e.g. 100 : 1) is created, it may be used to provide stereochemical control in a reaction with a substrate of intrinsically low D.S. (typically 1 - 5 : 1). Because such reagents not only enhance selectivity in a matched case, but override the intrinsic selectivity of a substrate in a mismatched case, the strategy in which they are used is called *reagent-controlled synthesis*. With regard to the aforementioned aldol reaction, reagent control was first achieved through modification of the ketone component (eq 2-4). For example, suppose ketone **31a** has a high D.S. in its reaction with aldehydes. If A* is removed subsequent to the condensation of **31a** and aldehyde **32a** to provide carboxylic acid **33d**, then the overall process is equivalent to acetate addition to an



31a **32a** **33a** **33d**

aldehyde to afford a β-hydroxy carbonyl compound. Note that the sense (*R* or *S*) of the stereogenic center is controlled by proper choice of A* which is covalently bound to the product **33a**. Reagents that function in this capacity are called *internal chiral reagents*, and many are available which meet the criteria for reagent-controlled synthesis.[27]

A more difficult problem is faced when the stereochemical features of both A* and B* are part of the target molecule and are therefore prefixed. A solution to this problem is of great significance since multi-step organic synthesis becomes markedly more efficient if conducted in a convergent manner. Without such a solution, the inability to predict the ratio of diastereomers, or even the major diastereomer, when complex fragments are coupled, presents a major risk to those who include such a reaction in a synthetic design. A general approach to this problem is the use of a third chiral component which is capable of modifying the apparent D.S. of either chiral reactant. For example, in the aldol reaction, let us choose to modify the enolate of chiral ketone **31a** with chiral metal reagent **35** (eq 2-5). If the C* moiety can affect the enolate D.S. in such a manner as to provide



31a **33a**

excellent selectivity for either diastereomer [e.g. for **33a** over **34a** (see eq 2-3)], then the aldol coupling of methyl ketones and aldehydes, accompanied by the creation of a stereogenic center, becomes routine. Note that C* does not appear in the product.

Reagents that mediate reactions in this manner are called *external chiral reagents*.[28] During the bryostatin project, we opted to test the viability of effective aldol fragment-coupling reactions with the available reagents. For such aldol reactions, however, external chiral reagents capable of providing the desired stereochemistry in the mismatched case, the most challenging criterion for reagent-control, still remain elusive.

2.4 Credits for Chapters 3 through 8

The total synthesis of bryostatin **7** involved several collaborators. In order to provide a comprehensive story of this undertaking, Professor Masamune has requested that the description of pertinent experiments carried out by co-workers be included in this thesis. Acknowledgement of these contributions is given throughout the text.

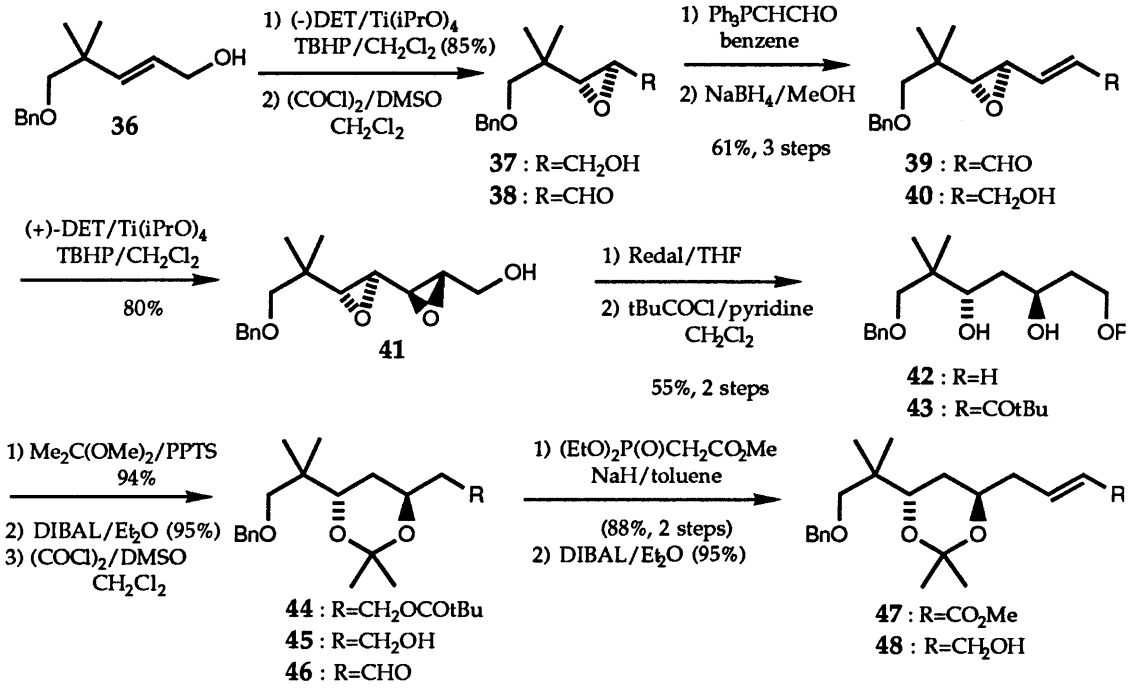
Chapter 3

Synthesis of Fragment A

3.1 Linear Synthesis of Fragment A

An early route to fragment A (**25**) (Scheme 3-1) utilized the reductive ring-opening of epoxy alcohols by Redal* to provide 1,3-diols, a method previously developed in our laboratories in collaboration with Professor Sharpless' group.[29] This reaction sequence has already been detailed by Dr. David C Whritenour,** and is presented here for its comparison with the convergent synthesis developed by the author. Dr. Whritenour's route is summarized as follows. The epoxidation of allylic alcohol **36** afforded **37** (85%, 92%ee) which, after oxidation to aldehyde **38**, olefination,

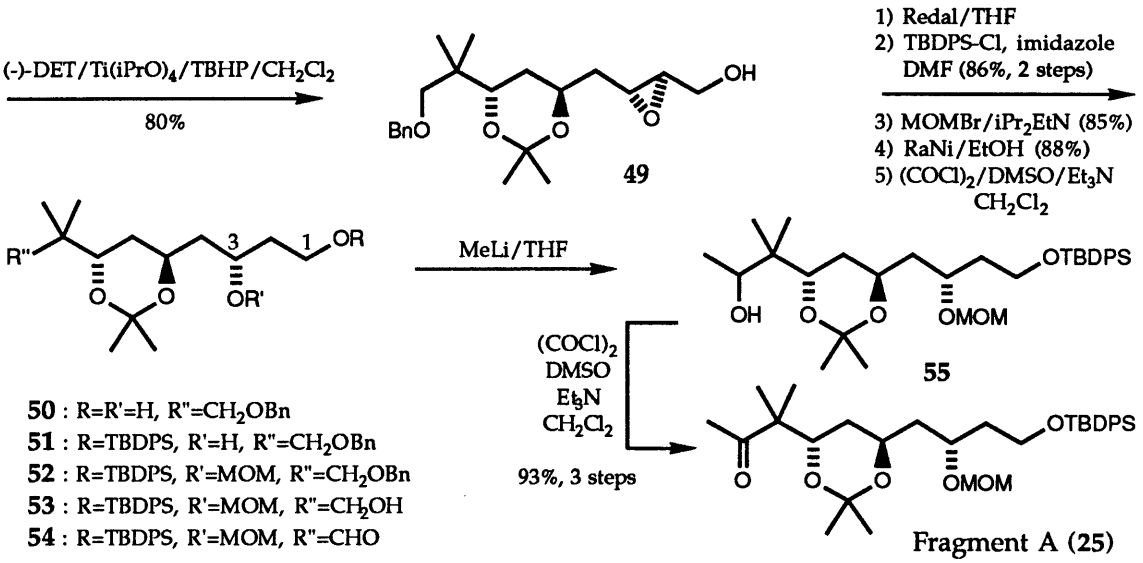
Scheme 3-1



* sodium bis(2-methoxyethoxy)aluminum hydride

** A complete discussion can be found in the preceding thesis concerning the bryostatin project: Whritenour, D.C.; Ph.D. Thesis, MIT, 1987.

Scheme 3-1 (cont.)



50 : R=R'=H, R''=CH_2OBn
51 : R=TBDPS, R'=H, R''=CH_2OBn
52 : R=TBDPS, R'=MOM, R''=CH_2OBn
53 : R=TBDPS, R'=MOM, R''=CH_2OH
54 : R=TBDPS, R'=MOM, R''=CHO

and reduction, was converted to allylic alcohol **40** (61%, 3 steps). The epoxidation that followed afforded bisepoxide **41** (80%, >98%de). Directed double ring-opening by treatment with Redal[29] followed by hydroxyl group differentiation led to alcohol **45** (50%, 4 steps). An analogous sequence of Swern oxidation,[30] Horner-Emmons olefination,[31] reduction, epoxidation, and ring-opening yielded diol **50** (65%, 5 steps). Subsequent protection of the C(1)- and C(3)-alcohols, and debenzylation afforded C(9)-alcohol **53** (64%, 3 steps) which was converted to the C(9)-ketone, fragment A (**25**) (71%, 3 steps).

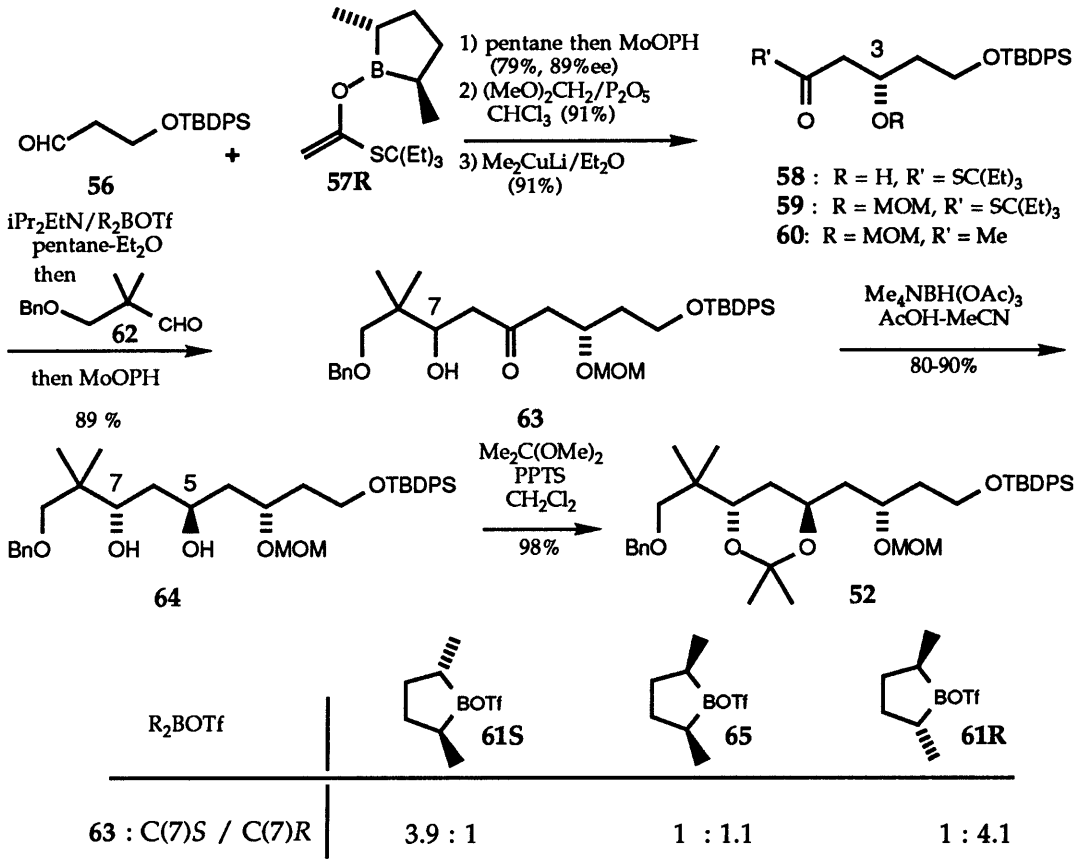
Although each step of Scheme 3-1 proceeded smoothly to afford a product of *secured* stereochemical assignment (which was ultimately used to confirm the stereochemistry of **52** from the alternative route), the attainment of a less lengthy sequence was also desired.

3.2 Convergent Synthesis of Fragment A

It seemed most appropriate that the problems associated with the linear synthesis of fragment A (**25**) be remedied by an application of stereoselective aldol

methodology developed in our group.[21] A convergent synthesis with less than half the steps of Scheme 3-1 was designed which exploited the strategy of double asymmetric synthesis.[25] Thus, ketone **25** was divided into two fragments of minimal complexity and the execution of this plan is detailed below (Scheme 3-2). Aldehyde

Scheme 3-2



56[32] was converted to thioester **58** with boron enolate reagent **57R**[21](79%, 89% ee as determined by ^{1}H NMR of the corresponding Mosher's ester[33]). Treatment of **58** with methoxymethyl bromide in N,N-diisopropylethylamine led to low yields of methoxymethyl ether **59** (40-50%).[34a] Similarly, treatment of **58** with sodium hydride/methoxymethyl bromide in THF also provided a low yield of the desired compound (30-40%).[34b] A major byproduct formed under these latter conditions contained no thiol group and was spectrally consistent with the corresponding β-

lactone.[35] Desired protection of the C(3)-alcohol moiety under basic conditions appeared not to be feasible, and acidic conditions were considered. It was ultimately found that treatment with dimethoxymethane and phosphorous pentoxide in chloroform completed this task satisfactorily (91%).[34c] Conversion to methyl ketone **60** ensued upon treatment with lithium dimethylcuprate (94%).[36]

In the subsequent coupling reaction, external chiral reagent **61S**,[21] selective for the desired stereochemistry, was utilized. Thus, the boron enolate derived from **61S** and **60** was condensed with aldehyde **62**[37] to provide **63** (87%) as an inseparable mixture of C(7)-diastereomers, the ratio of which could not be determined by HPLC analysis or ^{1}H NMR of either **53** or its corresponding acetate and Mosher's ester[33] derivatives. After considerable effort was made to ascertain the product ratio for this aldol reaction, the two diastereomers were found to be easily differentiated subsequent to the step that followed. Thus, directed reduction of this mixture with the Saksena-Evans reagent*,[38] led to **64** (86%) as a 3.9 : 1 mixture of chromatographically separable and ^{1}H NMR-distinguishable diastereomers. Mediation of the aldol reaction by an achiral reagent (*meso*-boranyl triflate **65**),[21b] and subsequent reduction afforded **64** as a 1 : 1.1 ratio of diastereomers. Predictably, the use of **61R**, selective for the undesired diastereomer, led to a 1 : 4.1 ratio. Thus, the diastereomeric ratio of **64** was apparently a reflection of the ratio obtained in the aldol reaction (rather than the reduction). In these coupling reactions, ketone **60** behaves like an achiral methyl ketone and the C(7)*S* / C(7)*R* ratios in the matched and mismatched reactions are simply the diastereofacial selectivity of the chiral reagent, **61R** or **61S** (apparent single asymmetric synthesis). The synthesis of **52** was completed by acetonide formation on diol **64** (98%), and the C(7)- and C(5)-

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* tetramethylammonium triacetoxyborohydride

stereochemistry was confirmed by comparison with compound **52** prepared via the route described earlier in Scheme 3-1.

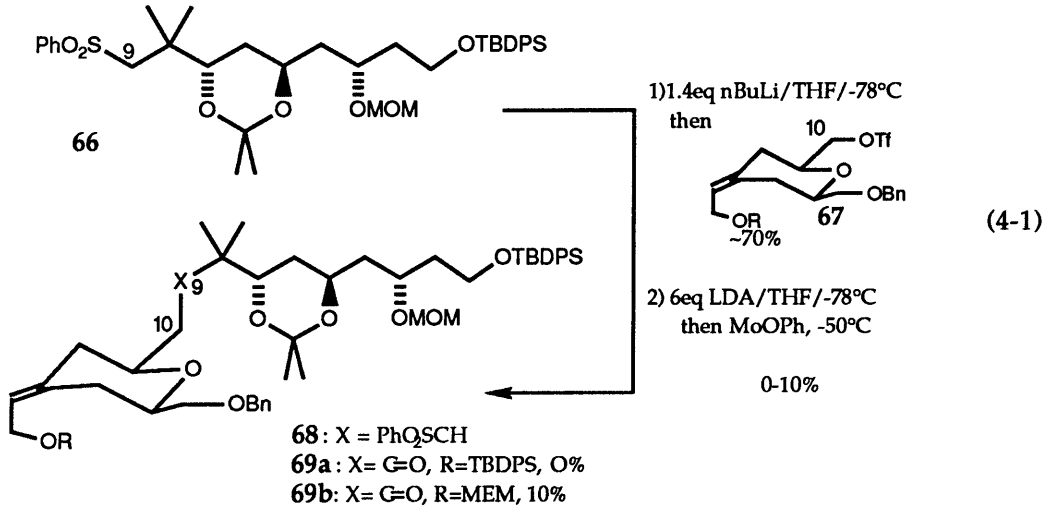
As illustrated in this chapter, even for fragments of moderate complexity, a convergent syntheis is much shorter than a linear synthesis. The fact that we could achieve acceptable, albeit modest stereoselection in our execution of the convergent synthesis of fragment A(**25**), strongly emphasizes the urgent need for more powerful external chiral reagents.

Chapter 4

Synthesis of Fragment AB

4.1 Selection and Synthesis of Fragment B

In our earliest studies on the synthesis of fragment AB (**21**, section 2.1), the more usual connection was made between C(9) and C(10) (eq 4-1), and although the



(4-1)

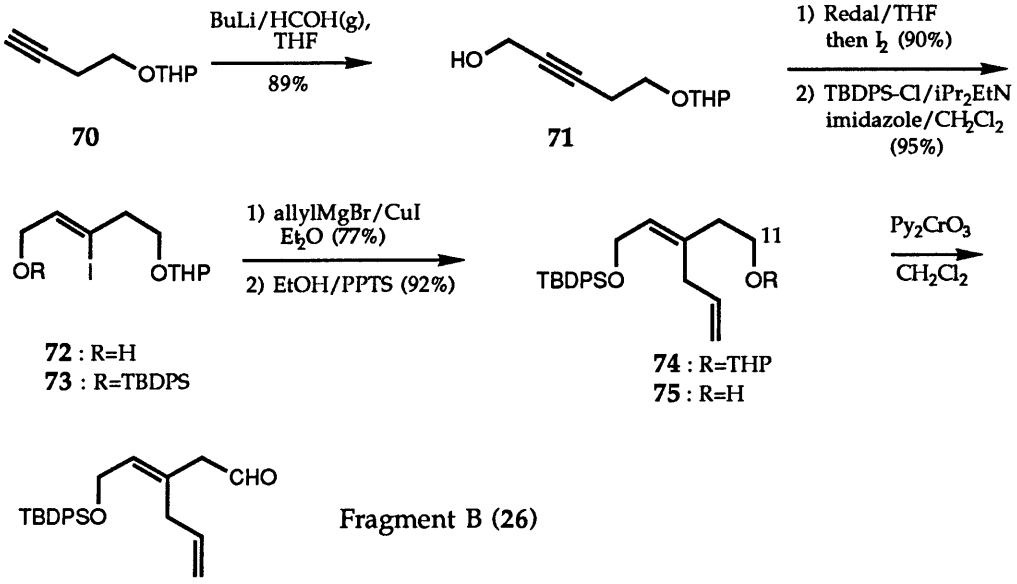
reaction between triflate **67** and lithiated sulfone **66** proceeded well, affording sulfone **68**,[39] the subsequent oxidation to desired ketone **69** proved problematic (0-10% yield depending on the R-protecting group).[40] Although this original route was abandoned, the diastereomerically pure product obtained in this way was used to confirm the stereochemistry at C(11), subsequently created via the aldol route described in this chapter.* It should be noted that the aldol methodology ultimately necessary for the coupling of the A and B fragments also greatly reduced the complexity of the B fragment. Specifically, while 14 steps were required for the

* This original approach to the coupling of fragments A and B has been detailed by Dr. David C. Whritenour (Whritenour, D.C.; Ph.D. Thesis, MIT, 1987) as has been the confirmation of the C(11)-stereochemistry via this method.

preparation of triflate **67** from *S*-malic acid,[41] only seven steps are required for the preparation of aldehyde **26** (see Scheme 4-1) from 3-butyn-1-ol.

An efficient synthesis of fragment B (**26**),* one amenable to large-scale preparation, was developed by the author as follows (Scheme 4-1). Treatment of

Scheme 4-1



alkyne **70**[42] with *n*-butyllithium in THF and subsequent exposure of the derived anion to gaseous formaldehyde afforded alcohol **71** (89%). Initially, preparative (40 g) scale execution of this reaction led to a low conversion of starting material. This problem was solved, however, by regulating the flow of formaldehyde such that it remained slow and continuous throughout the reaction.

Reduction of the propargylic alcohol moiety in **71** with Redal**,[43] provided a single product by TLC (presumably the aluminate ester) which was easily converted to

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* Aldehyde **26** was first synthesized by Dr. Masanori Kageyama (in a less efficent manner) to test the feasibility of the aldol reaction between fragment A (**25**) and B (**26**) (see section 4.2).

** sodium bis(2-methoxyethoxy)aluminum hydride

iodide **72** upon in situ treatment with iodine. Subsequent protection of the crude iodide with *tert*-butyldiphenylsilyl (TBDPS) chloride,[18] followed by copper-catalyzed allylation, led to diene **74** (78%, 3 steps) via iodide **73**. When this allylation step was performed directly on alcohol **72** (rather than on **73**) and was followed by protection of the crude product with TBDPS-chloride, the desired product (**74**) was obtained in much lower yield (35-40%). This process also led to higher and lower R_f products that eluted very closely to **74** on silica gel. The disparity in efficiency between allylation-protection versus protection-allylation is presumably due to the relative propensity of iodide **72** to decompose. For example, while **72** is air and light sensitive, silyl ether **73** is unaffected even after 78 h exposure to air and incandescent illumination, neat or dissolved in chloroform.

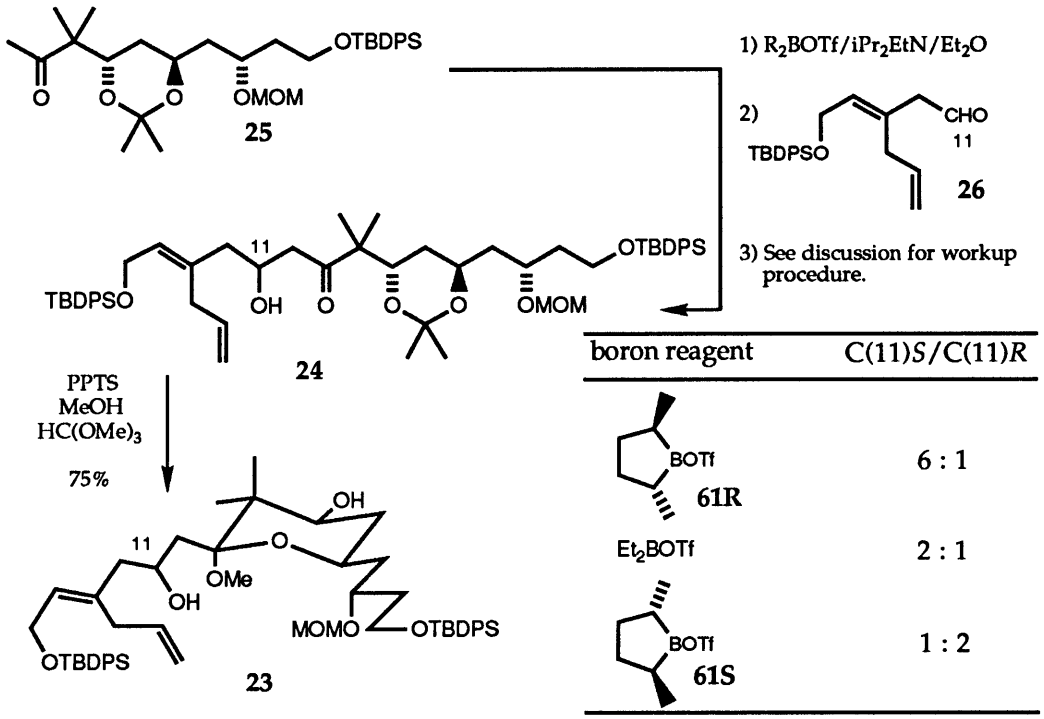
Removal of the O(11)-THP moiety was accompanied by a 5-20% loss of the TBDPS-group when pyridinium *p*-toluenesulphonate was used in methanol. This problem was most easily circumvented by use of ethanol as a solvent, which led to alcohol **75** in 92%. Initial application of the Swern oxidation[30] afforded aldehyde **26** accompanied by α,β-unsaturated byproducts. During chromatographic purification of **26**, however, decomposition occurred and the overall yield was unacceptable. Analysis by TLC of the corresponding Collins oxidation[44] product suggested similar impurities, which fortunately turned out to be an artifact of the analytical method. Indeed, fragment B (**26**) prepared in this way was >95% pure by ^{1}H NMR and was (necessarily) used without purification.

4.2 The Coupling of Fragments A and B

In the connection of methyl ketone **25** and aldehyde **26** (Scheme 4-2), mediated by an achiral metal, the product ratio would depend solely on the diastereoselectivity of **25**, unpredictable in both magnitude and sense, a situation encountered in the

assembly of **60** and **62** (see section 3.2). As in the earlier case, our strategy was to externally alter this selectivity by exploiting the predictable stereochemical outcome associated with the aldol reaction of 2,5-*trans*-dimethylborolanyl enolates.[21b] Preliminary experiments, conducted by Dr. Kageyama, uncovered the ratio of diastereomers that resulted in the connection of **25** with **26**, mediated by boron reagents. His results are summarized briefly below (Scheme 4-2). Reaction of **26** with

Scheme 4-2



the enolate derived from **25** and **61R**[21] provided β-hydroxy ketone **24** as a mixture of inseparable diastereomers which could not be distiguished by ^{1}H NMR except at the [O(11)]-proton. The first pyran cyclization, which ensued upon deacetonization in methanol, afforded methyl acetal **23** (84%) as a 6:1 ratio of separable diastereomers. Mediation of the aldol reaction by an achiral reagent (diethylboryl triflate)[45] and subsequent pyran formation afforded **23** as a 2:1 ratio of diastereomers. Predictably, the use of **61S**, selective for the undesired stereochemistry, led to a 1:2 ratio. Thus, the

diastereomeric ratio of **23** was a result of the stereoselectivity displayed by the aldol reaction (rather than the pyran-ring formation). Note that the desired stereochemistry is obtained by the complimentary selectivities of **25** and **61R** (a matched case). Furthermore, the above ratios of diastereomers observed for both the matched and mismatched pairs are in accord with the approximate multiplicativity rules of D.A.S.[25]

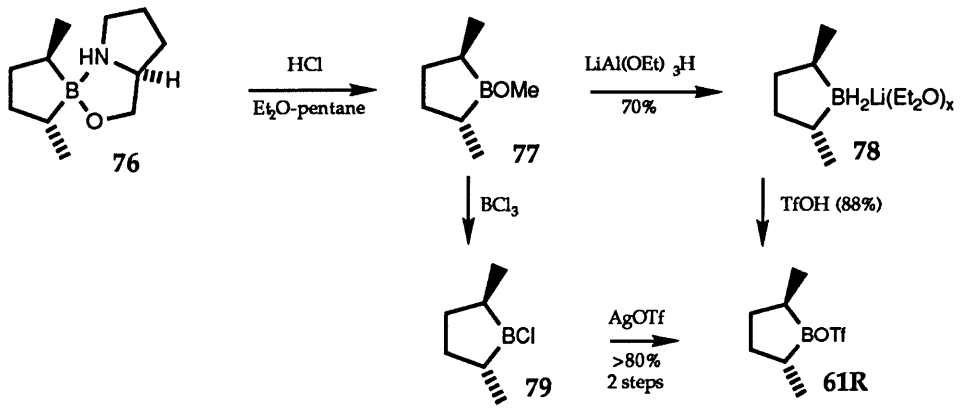
With the *stereochemical* efficiency of the coupling reaction secured, the author set out to verify its *preparative* efficiency. The yield of this crucial step was acceptable based on ketone **25**, but there remained two major problems: more than one equivalent of aldehyde **26** and (more importantly) two equivalents of reagent **61R** were needed. After minor advances in the optimization of this aldol process, it was found that the use of pure (but not chromatographed) aldehyde **26** solved both of these problems. Apparently, the second equivalent of **61R** served only to sequester an impurity present in the chromatographed fragment B aldehyde.

A second area of improvement concerned the high cost of **61R**. It was desired that this borolanyl triflate be prepared from its aminoalcohol complex **76**[21] in the most efficient way possible and that it be recycled. The original method of converting methoxyborolane **77** to **61R** (Scheme 4-3), which involved lithium borohydride **78** as an intermediate, has been detailed by Dr. Byong-Moon Kim.* Dr. Kim's route required that methoxyborolane **77** be treated with *precisely* two equivalents of triethoxylithium aluminum hydride. The resulting borohydride (**78**) was then converted to the triflate by treatment with *precisely* two equivalents of triflic acid. The overall yield of these two steps can be as high as 60%, but varies significantly, presumably due to the capricious nature of the reductive step. The

* Kim, B.-M.; Ph.D. Thesis, MIT, 1987.

more efficient route that was developed for preparative scale synthesis of **61R** involved chloroborolane **79** (Scheme 4-3) as an intermediate, prepared by treatment

Scheme 4-3



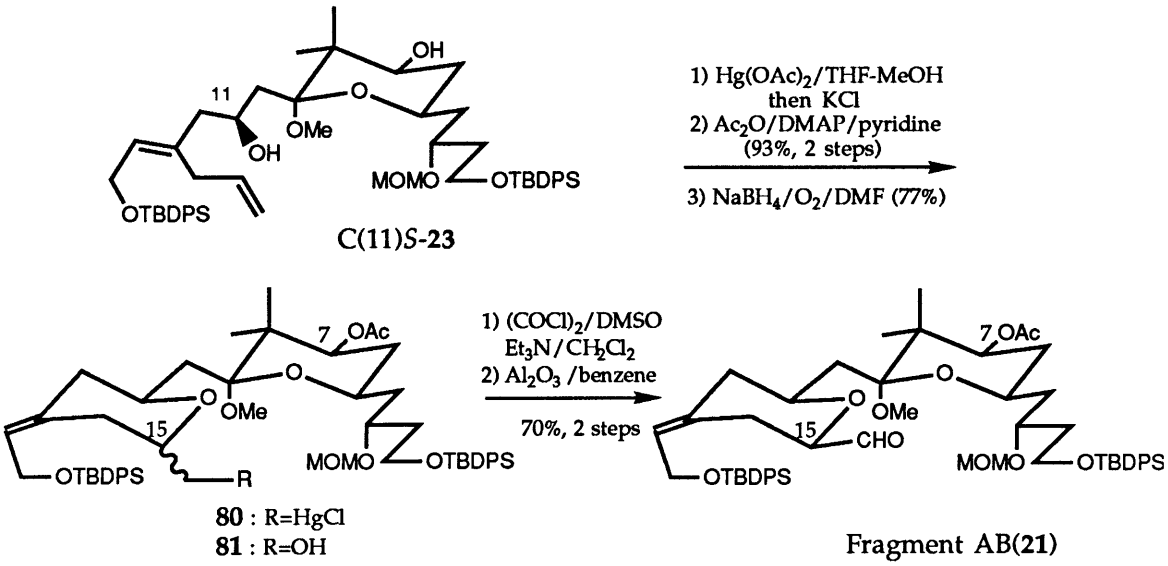
of methoxyborolane **77** with boron trichloride.[46] Treatment of **79** with silver triflate in pentane at 0°C completed the conversion, consistently providing **61R** in greater that 80% yield from **77**.

In order to recycle this expensive reagent (**61R**), the usual oxidative workup procedure of the aldol reaction (which destroyed the 2,5-*trans*-borolanyl moiety)[21] had to be replaced. Application of an aminoalcohol workup developed for the reaction of aldehydes with the boron enolates of thioacetates,[21] allowed for 75-85% recovery of the aminoalcohol complex. Conversion of this complex back to the triflate could be accomplished (as in Scheme 4-3) in 80% yield. Thus, the amount of this chiral borolane *consumed* in the aldol reaction was ultimately reduced by 80% (0.4 equivalents versus two equivalents).

4.3 Completion of Fragment AB

The synthesis of the AB fragment was completed by a second pyran formation on methyl acetal **23** (Scheme 4-4). This stereorandom cyclization was triggered by treatment with mercuric acetate[22] to afford an organomercurial intermediate which,

Scheme 4-4



80 : R=HgCl
81 : R=OH

Fragment AB(**21**)

after acetylation of the C(7) alcohol, yielded **80** (85%). Oxidative demercuration led to alcohol **81** (75%)[47] and Swern oxidation[20] afforded aldehyde **21** (85%) as a 1:1 equatorial-axial mixture at C(15). Subsequent equilibration to a 9 : 1 equatorial-axial mixture of aldehydes was effected by stirring with aluminum oxide in benzene, thereby completing the synthesis of fragment AB (**21**).

4.4 Summary

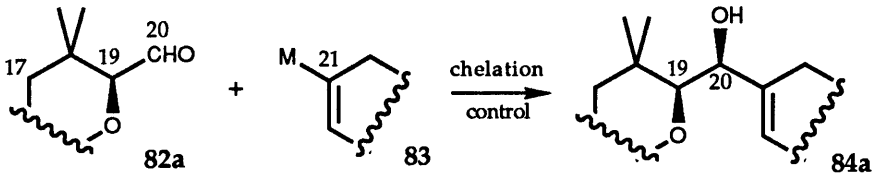
External chiral reagent control proved to be of paramount importance in the development of an efficient connection of the A and B fragments. Good selectivity (6:1) and high efficiency (>85% yield) was displayed in this critical aldol reaction.

Chapter 5

Synthesis of Fragment CD

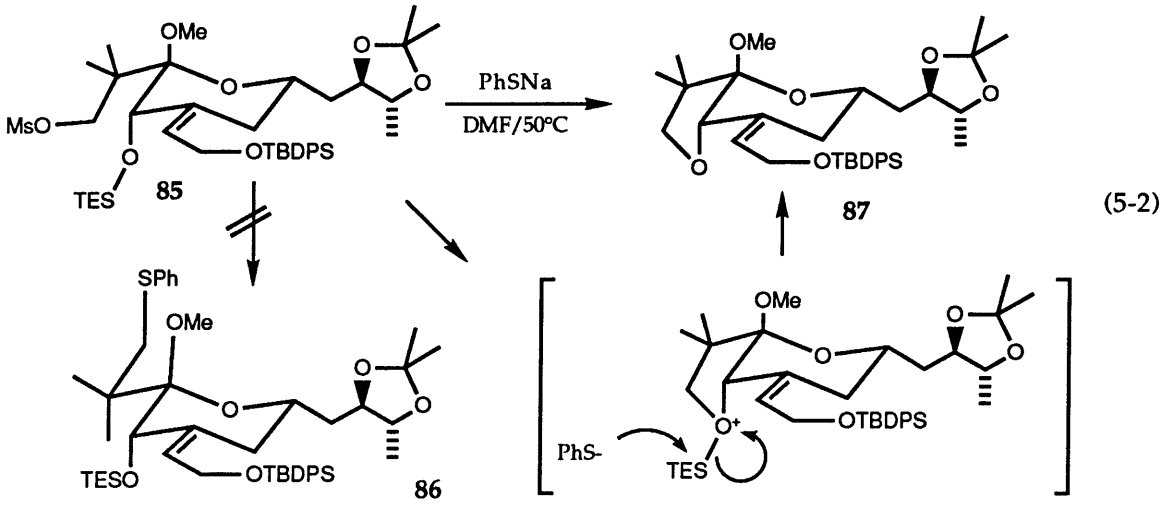
5.1 Selection of Fragment C

The coupling of a fragment C aldehyde (e.g. **82**, eq 5-1) with a metallated fragment D olefin (e.g. **83**) returns this discussion to the convergent, stereoselective



assembly of fragments in which carbon-carbon bond formation is accompanied by the creation of a stereogenic center. In sharp contrast to our use of external chiral reagent control to unite fragments A and B (Chapter 4), we planned to exploit metal chelation control (eq 5-1a)[24] to couple fragments C and D. Because the stereogenic center at C(19) is later converted to the ketone oxidation state, however, either configuration [C(19)*S* or (19*R*)] was a viable option, and thus good selectivity in the formation of either **84a** or **84b** was of equal utility. An advantage of this synthetic design was the structural simplicity of the [C(17)-C(20)]-segment, which allowed for many fragment C aldehydes to be examined in the C-D-coupling. Thus, the coarse- and fine-tuning capabilities of our strategy seemed to circumvent the normally capricious nature of chelation-controlled fragment coupling, but this reaction proved to be unexpectedly challenging. The experiments conducted in this area with C(17)-

oxygenated fragment C aldehydes have been detailed by Dr. David C. Whritenour* and are summarized here. Dr. Whritenour studied the use of both cyclic and acyclic aldehydes in their reaction with lithiated D fragments nucleophiles. He found that the acyclic, C(19)*S*-aldehydes were most stereoselective in this reaction [up to 6:1 C(20)*S*/C(20)*R* in good yield]. He also discovered that although THF was necessary for metalation of the D fragment, the addition of ether increased yields of the coupled product. From a study concerning the use of copper as an alternative metal for mediation of this reaction, he found that although selectivity was increased [up to 20:1 C(20)*S*/C(20)*R*], yields were much lower (30-45%). Thus, the lithiated fragment D was utilized preparatively. In Dr. Whritenour's final work on the synthesis of fragment CD, he observed that mesylate **85** could not be converted to its corresponding sulfide **86** (eq 5-2). Although the synthesis of neopentyl sulfides in



(5-2)

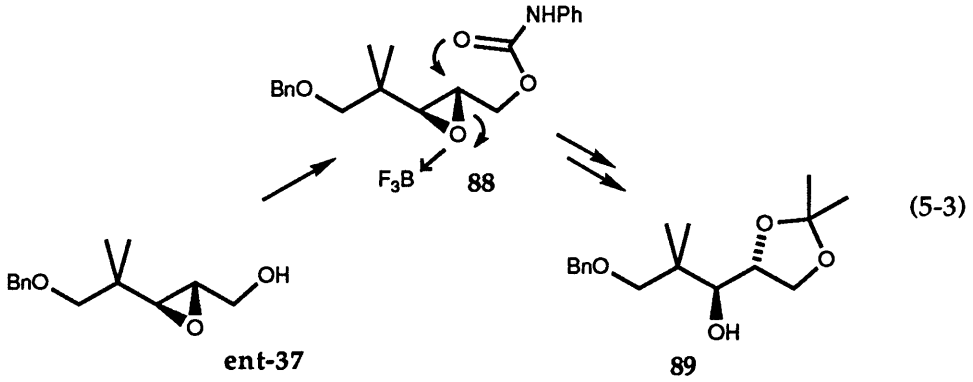
this manner is normally routine, it is reasonable that due to the release of steric congestion associated with the formation of furan **87**, this process competes extremely well with the desired transformation. Thus, the [C(17)-C(27)]-pyran

* A full discussion of the related experiments conducted prior to the author's involvement with the bryostatin project is presented in the preceeding doctoral thesis on this subject: Whritenour, D.C.; Ph.D. Thesis, MIT, 1987.

system, oxygenated at C(17), which resulted from the use of a C(17)-benzyloxy fragment C aldehyde, could not be elaborated to a utilizable product. This led to a revised scheme in which the C(17)-thiophenyl group was attached to fragment C prior to the C-D-coupling, as pursued by the author.

5.2 Synthesis of Fragments C

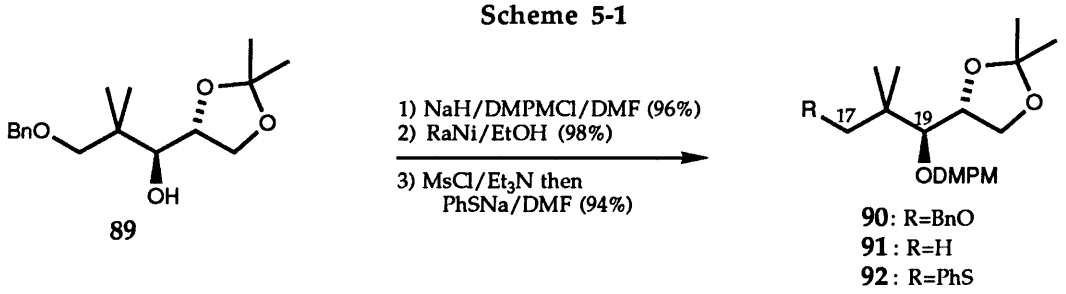
The C(17)-thiophenyl aldehydes could be synthesized from acetonide **89** (eq 5-3) for which an efficient synthetic route had already been established as part of the work described above. Most notably, this route includes the intramolecular epoxide



(5-3)

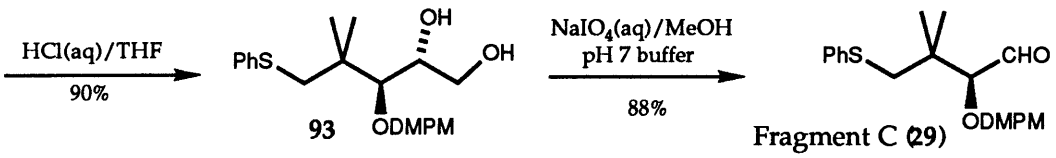
ring-opening on **88**.[48] Subjection of **89** to sodium hydride and 3,4-dimethoxybenzyl (DMPM) chloride in DMF smoothly led to hydroxyl protection at C(19) providing **90** (96%) (Scheme 5-1).[23] Hydrogenolysis of the benzyl ether in **90** using Raney nickel in ethanol led to alcohol **91** in 98% yield. Treatment of **91** with mesyl chloride/ triethylamine followed by nucleophilic substitution with sodium benzenethiolate in

Scheme 5-1



90: R=BnO
91: R=H
92: R=PhS

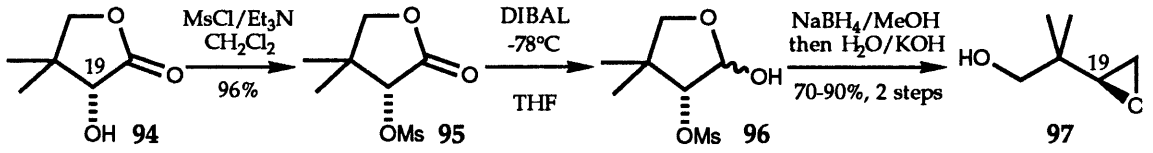
Scheme 5-1 (cont.)



DMF at 40°C led to sulfide **92** (94%). Hydrolysis of the acetonide moiety was achieved with 10 : 1 methanol/6N aqueous hydrochloric acid, to provide **93** in 90% yield. It is important to note that the DMPM-moiety was also prone to hydrolysis under these conditions and the reaction had to be carefully monitored. Periodate cleavage in pH 7 buffered methanolic solution afforded fragment C (**29**) (88%).

This 14-step synthesis of fragment C (**29**) probably does not represent the shortest route to this compound, although the general sequence followed served well as a venue to *all* of the aldehydes examined. In view of the structural similarity of **29** with pantolactone (**94**, Scheme 5-2), preliminary studies were

Scheme 5-2

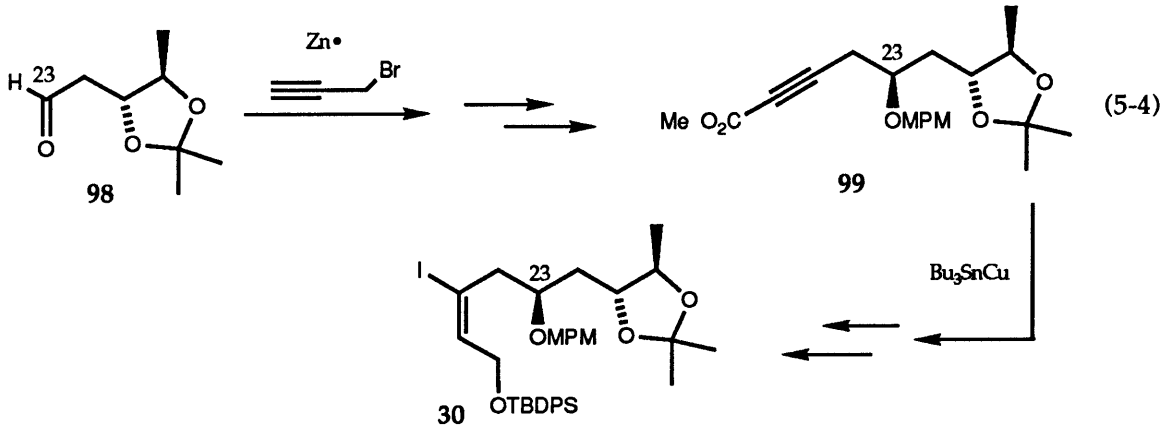


conducted which led to a potential precursor for C(19)*S*-**29** from C(19)*R*-**94**. Since a complete synthesis of **29** from the derived precursor (**97**) was not completed, this work is discussed only up to the step in which the C(19)-stereochemistry was inverted. Lactone **94** was treated with mesyl chloride/triethylamine to yield mesylate **95** as a stable crystalline solid (96%). Partial reduction of the lactone in **95** was accomplished with DIBAL* at -78°C to provide a 2 : 1 mixture of hemiacetal diastereomers (**96**). A second reductive step was performed with sodium

* diisobutylaluminum hydride

borohydride, and titration of the reaction mixture with aqueous potassium hydroxide afforded epoxyalcohol **97** in good yield. This C(19)*S*-epoxide could provide a shorter route to the C(17)-thiophenyl C fragment since the oxygenated center at C(17) is distinguished from those at C(19) and C(20) without the manipulation of protecting groups.

Our plan involved the coupling of fragment C (**29**) with fragment D (**30**). The synthesis of iodide **30** has also been detailed by Dr. Whritenour. Most notable in his



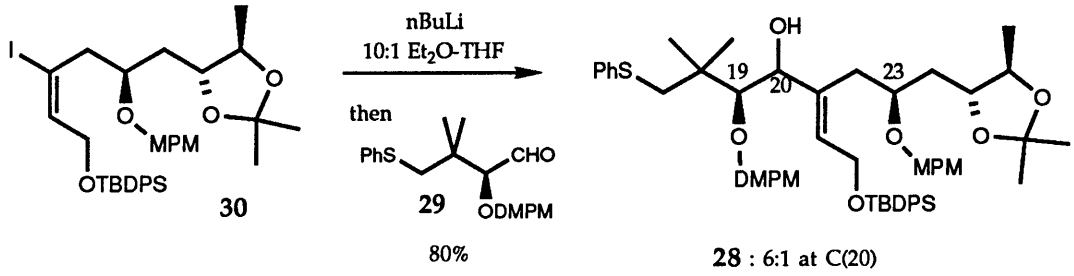
route is (i) the allenyl zinc chelation-controlled addition to aldehyde **98** to form the C(23)-stereogenic center in **99**,[49] and (ii) the conjugate addition of trialkyl tin copper to **99** to create the olefinic regiochemistry in **30**.[50]

5.4 Synthesis of Fragment CD

The chelation-controlled addition of organometallic reagents to α-alkoxy aldehydes has been a highly selective process in some cases.[51] The syn adduct is provided by chelation and subsequent nucleophilic addition along the Burgi-Dunitz trajectory[52] to the least hindered face of the aldehyde. These alkylations are known to be very sensitive to minor changes in the reaction conditions as Dr. Whritenour had indeed found with the C(17)-oxygenated fragment C aldehydes (see section 5.1).

Fortunately, the C(17)-thiophenyl aldehyde (**29**) behaved similarly to its C(17)-benzyloxy counterpart in the C-D-coupling to provide a 6 : 1 ratio of

Scheme 5-3

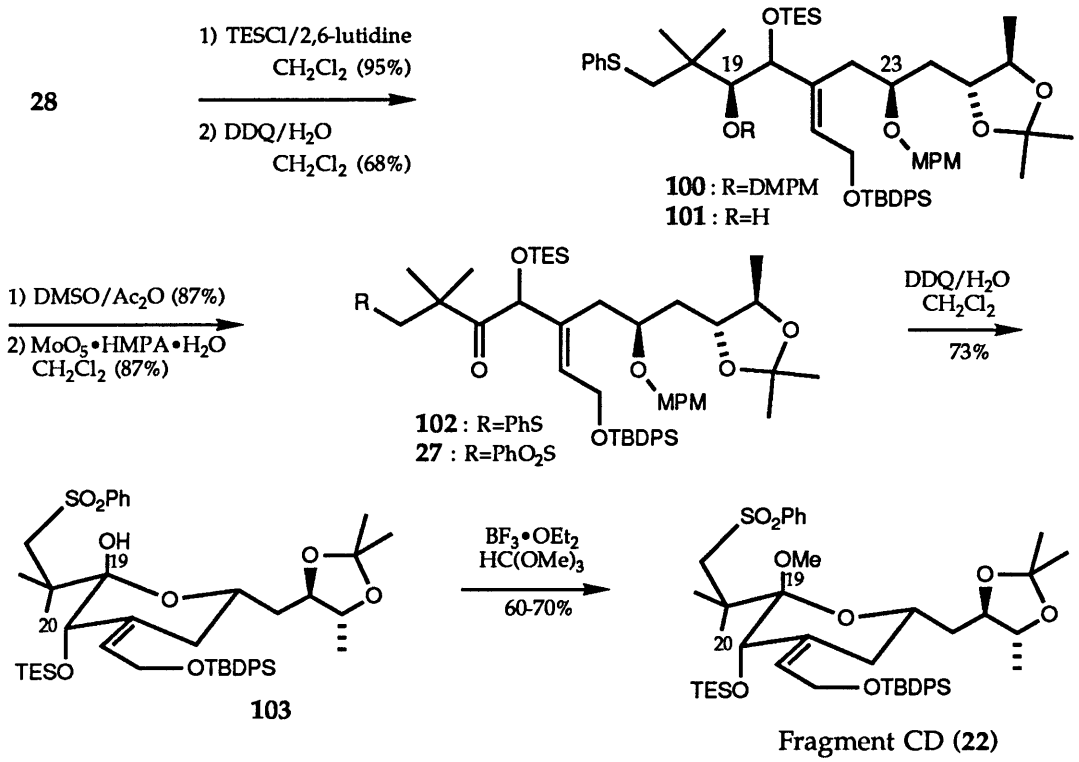


diastereomers **28** when performed in 10 : 1 ether/THF at -100°C (80%) (Scheme 5-3). The coupling constant $J_{19,20}$ (^{1}H NMR) of the corresponding acetate of **28** indicated that the desired syn diastereomer was the major product, an assignment that was correlated to previous work in which NOE studies were performed on a cyclic derivative of the C(17)-benzyloxy compound.

The synthesis of fragment CD from the coupled product required extensive optimization. Treatment of the 6:1 diastereomeric mixture of alcohol **28** with triethylsilyl (TES) triflate/lutidine[19] afforded silyl ether **100** (95%) (Scheme 5-4). It was known that DMPM ethers were more labile than the 4-methoxybenzyl (MPM) ethers, and that the rate of their oxidative conversion to the corresponding alcohols increased with steric congestion (e.g. secondary MPM-groups are removed in the presence of primary protecting groups).[23] Although both of these factors seemed to be in our favor, selective removal of the O(19)-DMPM group in the presence of the O(23)-MPM group proved to be a difficult task. The desired C(19)-alcohol (**101**) and the undesired C(19)-, C(23)-diol were isolated in approximately equal quantity (95% combined). Exaustive deprotection [to the C(19)-, C(23)-diol] followed by attempts at selective C(23)-protection led to an equally inefficient process. Acceptable selectivity

was achieved by exposure of **100** to one equivalent of DDQ* at 0°C for 30 min with rapid stirring, to afford **101** in 68% yield. The C(19)-, C(23)-diol and recovered **100**,

Scheme 5-4

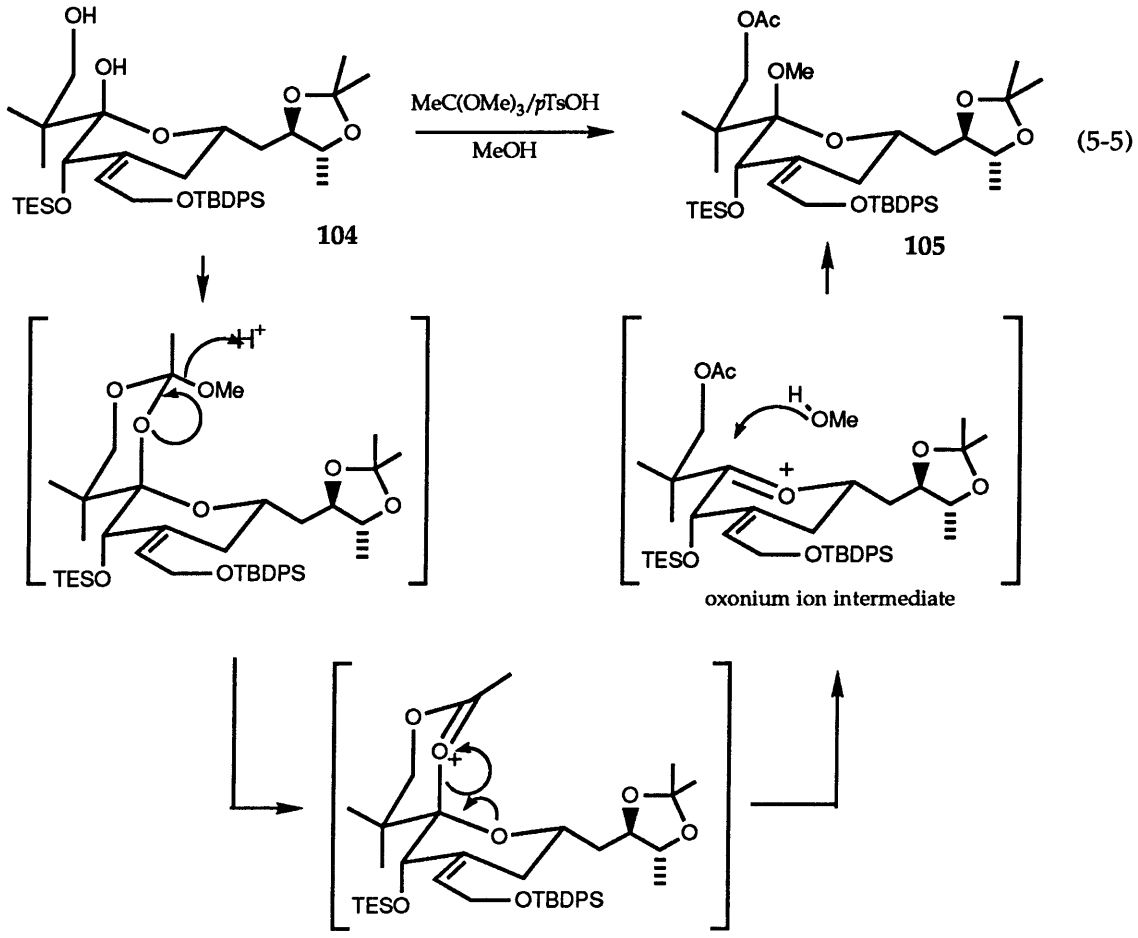


isolated in 8% and 12% yield respectively, were recycled. Oxidation first with DMSO/acetic anhydride[30] and then with oxodiperoxymolybdenum hexamethylphosphoramide monohydrate[53] led to sulfone **27** (76%, two steps) via sulfide **102**. The use of MoOPH**,[54] in this second oxidative step required longer reaction times and led to lower yields (~60%). Removal of the MPM-group and stirring over silica gel directly afforded C(19)-hemiacetal **103** (73%) which appeared to exist exclusively in this cyclic form; none of its acyclic precursor could be detected by ^{1}H NMR in either d-chloroform or d_6-benzene. The minor C(20)*R*-diastereomer,

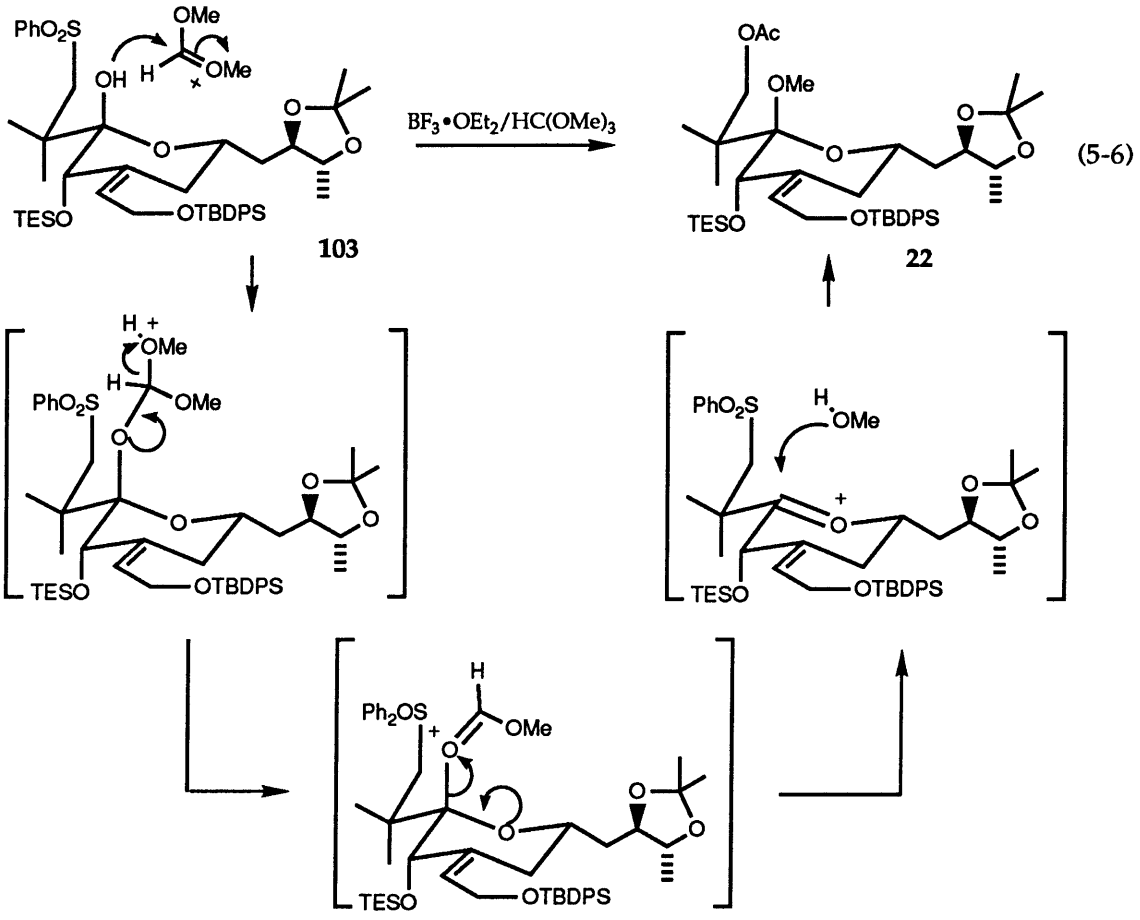
* 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
** oxodiperoxymolybdenum(pyridine) hexamethylphosphoramide

originating from the coupling reaction of the C and D fragments, was easily separated by silica gel chromatography at this stage.

Conversion of hemiacetal **103** to methyl acetal **22** proved to be very difficult. For example, treatment of hemiacetal **103** with acidic methanol, led to no methyl acetal formation, but instead to slow decomposition. Presumably, dehydration to the oxonium ion, necessary for incorporation of the methoxy group, is disfavored due to the steric hindrance associated with the large substituents of the pyran ring. Dr. Whritenour had previously shown (see eq 5-5) that conversion to such a congested methyl acetal was facile when (presumably) intramolecular assistance was operative, which indicated the feasibility of generating the oxonium ion intermediate. Because



the sulfone moiety of **103** is unable to participate in this special process, attention was turned to strongly dehydrating conditions. Successful conversion to methyl acetal **22** was first realized with trimethylsilyl (TMS) triflate/TMS-methoxide[55] albeit in modest yield (40-50%). This reaction was further encumbered by a varying degree of TMS-TES exchange at the C(20)-oxygen functionality. The addition of boron trifluoride etherate to a solution of hemiacetal **103** in trimethyl orthoformate effected this most difficult transformation more adequately, providing methyl acetal **22** in 60% yield, contaminated by a trace, inseparable impurity. In view of the possible mechanism for this process outlined in equation 5-6 (the *inter*molecular



version of equation 5-5) this reaction was optimized by a reversal of addition order (i.e. the hemiacetal was added last). This subtle change increased the yield of **22** to

69% and eliminated the production of the inseparable trace impurity. The stereostructure assigned to all the precursors of the CD fragment was confirmed by X-ray analysis of its C(20) hydroxyl compound generated from **22**.

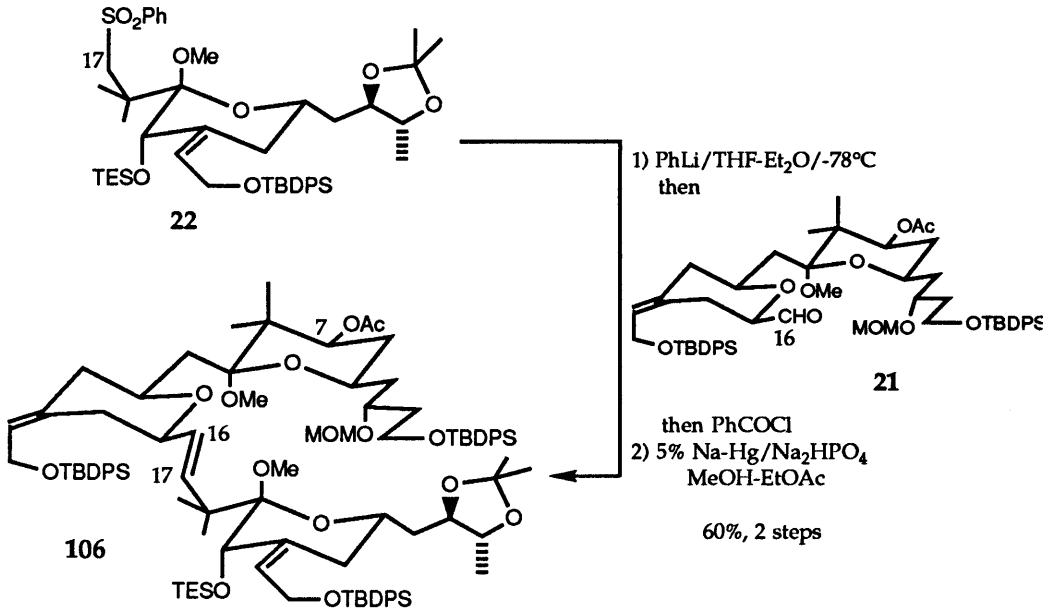
Chapter 6

Coupling of Fragments AB and CD and Attempted Conversion to Bryostatin 7

6.1 Coupling of Fragments AB and CD

Selective deprotonation of sulfone **22** at C(17), necessary for the Julia-Lithgoe olefination[20] between C(16) and C(17), proved difficult. This problem was solved by Dr. Masanori Kageyama, as summarized below. Dr. Kageyama found that treatment of sulfone **22** (Scheme 6-1) with *n*- or *tert*-butyllithium provided a mixture of

Scheme 6-1



neopentyl and arylic anions, as indicated by deuterium exchange, and that lithium diisopropylamide (LDA) led to little sulfone deprotonation. He ultimately discovered, however, that phenyllithium accomplished the desired metallation extremely efficiently,[56] and thus his attention returned to the remaining steps of the Julia-Lithgoe olefination.

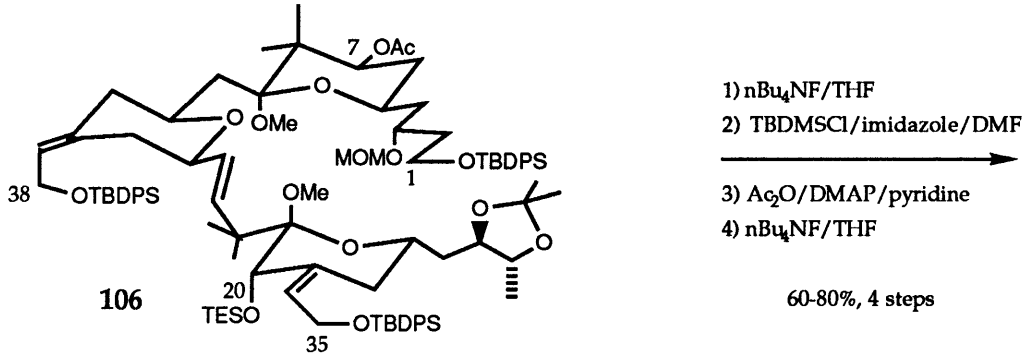
Fragment AB (**21**) was provided by the author (see Chapters 3 and 4). Aldehyde **21** was treated with C(17)-lithiated sulfone (**22**) to afford the C(16)-alkoxide which was esterified in situ. Subjection of the resulting crude mixture of

diastereomers to sodium amalgam effected reductive elimination to provide *E*-olefin **106** (60%, 2 steps). An initial problem encountered by Dr. Kageyama was hydrolysis of the C(7)-acetate moiety in this elimination step which he prevented by buffering the reaction mixture with dibasic sodium phosphate.[57]

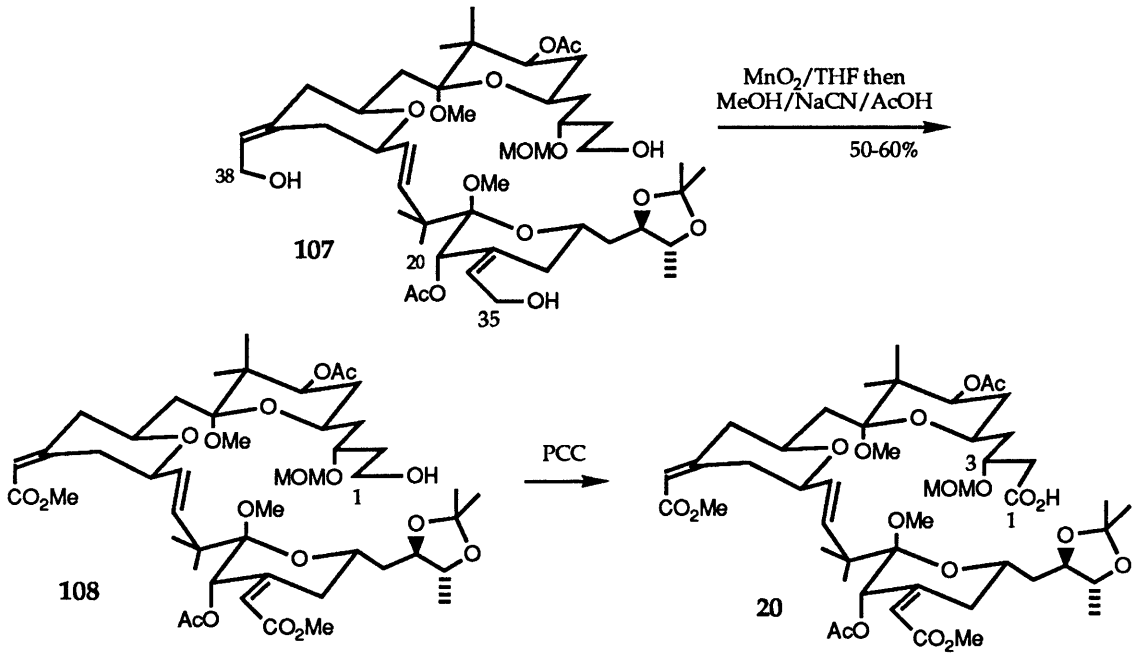
6.2 Elaboration to a Seco Acid Derivative and Unsuccessful Hydrolysis

With the seco acid framework in place, we were faced with the unanticipated instability of several advanced intermediates. For example, due to the poor selectivity Dr. Kageyama observed in the desilylation of **106** at O(20) (see Scheme 6-2), he pursued the alternative of exhaustive desilylation followed by selective silylation. This method of O(20)-differentiation proved more efficient, and he converted all of **106** to the tetraol. Upon overnight storage (neat at -6°C) this tetraol decomposed to a mixture from which no useful material could be salvaged. Ultimately, selective acetylation at C(20) was accomplished by (i) exhaustive desilylation, (ii) *immediate* selective silylation of the primary alcohols, (iii) C(20)-acetylation, and (iv) desilylation, without purification between steps (Scheme 6-2). The resulting C(20)-acetate (**107**) was found to be quite stable and oxidation of **107** to its corresponding bismethyl ester **108** (50-60%) with manganese dioxide/potassium cyanide in methanol[17] followed by chromium oxidation at C(1) provided protected seco acid **20**.

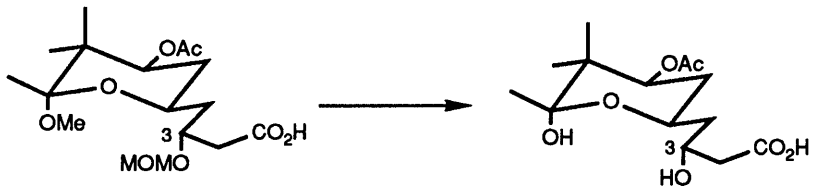
Scheme 6-2



Scheme 6-2 (cont.)

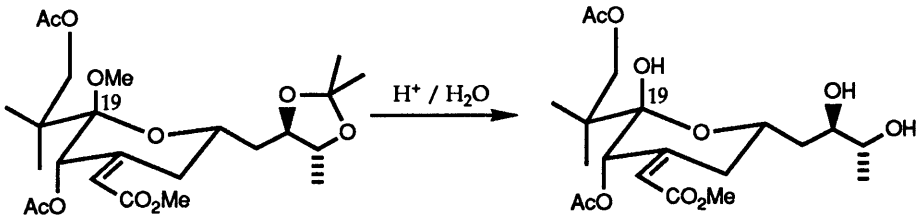


What remained for the synthesis of the free seco acid of bryostatin **7** was the hydrolysis of protecting groups, and it is appropriate at this point to mention our unusual choice of the methoxymethyl protecting group at O(3). As briefly mentioned (section 2.1), this protecting group was chosen judiciously. Specifically, Dr. Kageyama had found that the hydrolysis of a methoxymethyl ether was greatly facilitated when it was β to a carboxylic acid. For example, he was able to effect hydrolysis of this functionality from model compound **109** (eq 6-1) yielding **110** by utilizing either (i) 10 : 1 THF/6N hydrochloric acid or (ii) acetic acid.



109 **110** (6-1)

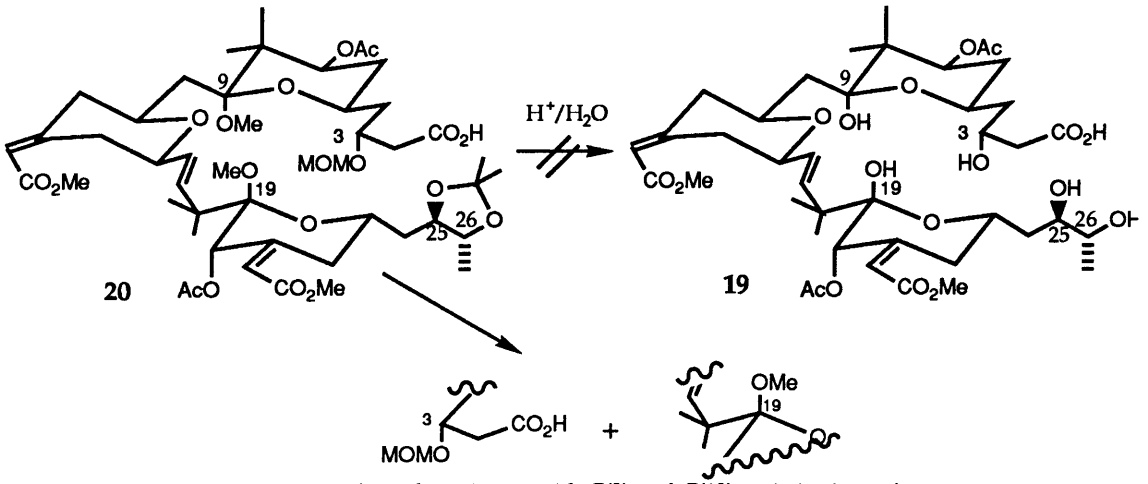
We had anticipated that the hydrolysis of the hindered C(19)-methyl acetal moiety might also present a problem. A model study conducted due to this concern indicated that there would be no such difficulty (eq 6-2) since methyl acetal **111** was hydrolyzed to hemiacetal **112** under the same conditions utilized for the removal of the C(3)-methoxymethyl group from model systems (e.g. **109**, eq 6-1).



111 **112** (6-2)

The protected seco acid, however, did not behave as anticipated. Unfortunately, exhaustive attempts at complete hydrolysis of the protecting groups of **20** [at O(3), the C(9)- and C(19)-acetals, and the O(25)-O(26) acetonide] invariably led to intractable mixtures in which there was no detectable quantity of **19** (Scheme 6-3).

Scheme 6-3



(complex mixture with C(3) and C(19) moieties in tact)

Very often, crude ^{1}H NMR spectra of the generated mixtures indicated a considerable amount of byproducts in which the C(3)-methoxymethyl ether and/or the C(19)-methyl acetal remained intact. It is difficult to explain the anomalous stability of the β-hydroxy protected carboxylic acid moiety in seco acid derivative **20**. With

regard to the C(19)-methyl acetal, however, it is worth noting that the model system shown above (eq 6-2) contains a C(17)-acetate moiety which may have assisted the process of methyl acetal hydrolysis.

6.3 Summary of Chapters 3 through 6

In this first synthetic approach to the seco acid of bryostatin **7**, efficient routes to all the fragments (A, B, C, and D) were developed, and the feasibility of fragment coupling with concomitant creation of a stereogenic center was established in the union of fragments A and B, and that of fragments C and D. Furthermore, conditions for the Julia-Lithgoe olefination were secured. The fact that liberation of the C(3)-alcohol group and the C(19)-hemiacetal moiety could not be accomplished, however, was very disappointing, and this failure demanded that we revise our synthetic approach.

Chapter 7

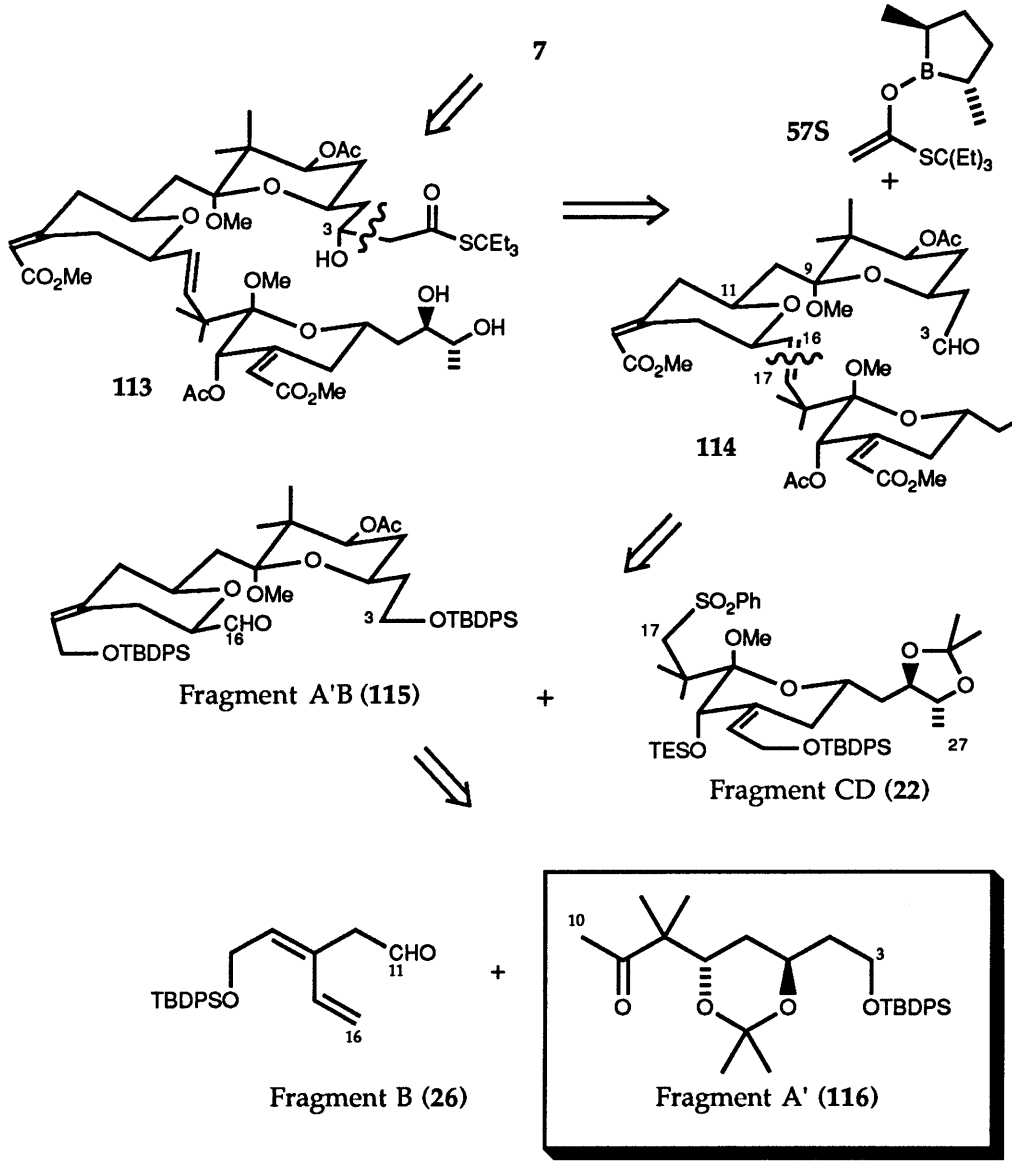
Revised Plan for the Synthesis of Bryostatin 7

7.1 Revised Retrosynthetic Analysis

We set out to modify our original synthetic scheme for bryostatin **7**. This original approach had led us to a protected seco acid derivative from which the O(3)-methoxymethyl group could not be hydrolyzed (see section 6.2). Our planned modification initially focussed on the use of an alternative protecting group at O(3). The requirements for such a protecting group, however, to survive the many synthetic manipulations leading to the O(3)-protected seco acid *and* be easily removed to provide the C(3)-alcohol, were difficult to meet. Therefore, our attention turned to an aldol reaction with a C(3)-aldehyde {seco-acid minus the [C(1)-C(2)]-subunit} which would directly create a C(3)-hydroxyl, seco acid derivative. For this aldol reaction, performed at very a late stage of the synthesis, we required a chiral acetate equivalent which reacted with high selectivity and under mild conditions. The boron-mediated aldol condensation between aldehydes and acetic acid thioesters, as developed in our group,[21] met these criteria. Moreover, the consistent behavior of this aldol methodology with respect to double asymmetric synthesis ensured that significant C(3)*R*-selectivity could be attained.[26] That the resultant thioester moiety might be employed directly in macrolactonization by the use of a thiophilic metal cation was also appealing.[58]

Thus, in our modified retrosynthetic analysis (Scheme 7-1), we planned to form bryostatin **7** from seco acid derivative **113** (directly or via the carboxylic acid) which, in turn, was envisaged as arising from an aldol reaction between aldehyde **114** and chiral acetate equivalent **57S**.[21] Disconnection at the [C(16)-C(17)]-olefin (as before, section 2.1) led to fragment A'B [**115**, C(3)-C(16); note that " A' " is used in

Scheme 7-1

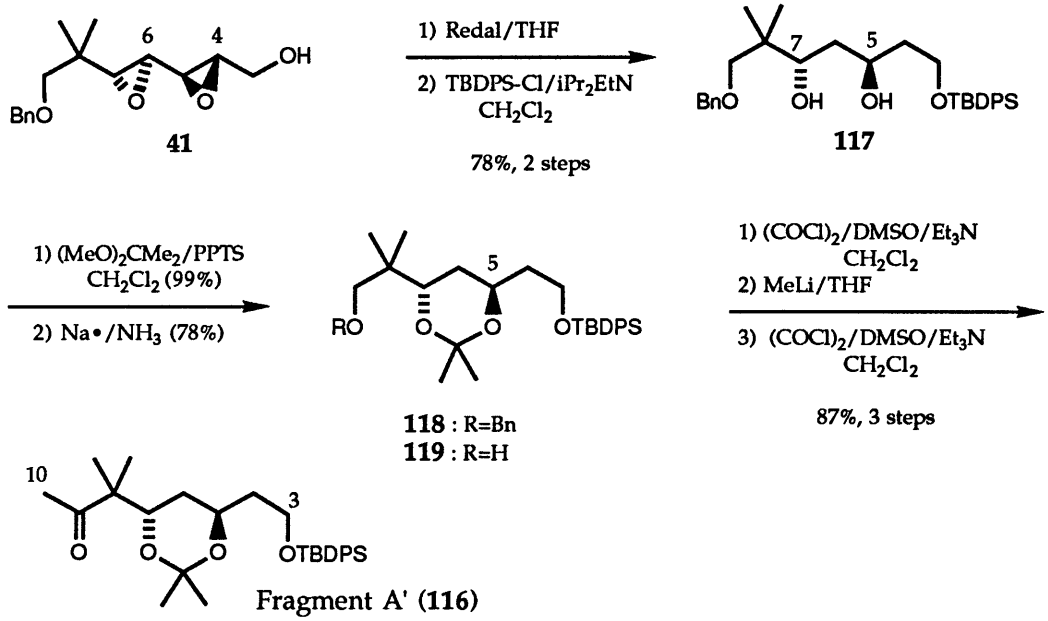


place of " A " to convey the lack of C(1) and C(2)] and fragment CD (**22** : synthesis discussed in Chapter 5). The retrosynthesis of aldehyde **115** followed analogously to that of its [C(1)-C(16)]-counterpart to provide fragment A' [**116**, C(3)-C(10)] and fragment B (**26** : synthesis discussed in section 4.1). The synthesis of ketone **116** and ultimately fragment A'B (**115**) was pursued by the author.

7.2 Synthesis of Fragment A'

Fragment A' (**116**) was amenable to the linear epoxide ring-opening methodology[20] used in the original synthesis of fragment A (**25**, see Chapter 3). Whereas 25 steps were necessitated by this strategy to prepare the [C(1)-C(10)]-subunit from 2,2-dimethyl-1,3-propanediol, ketone **116** was produced in only 16 steps. Bisepoxide **41** was treated with Redal* in THF (as before, see section 3.1) and protection of the crude triol with *tert*-butyldiphenylsilyl (TBDPS) chloride[18] led to diol **117** in 78% overall yield from **41** (Scheme 7-2). The [C(5)-C(7)]-acetonide was

Scheme 7-2



easily incorporated to form **118** (99%). Treatment with Raney nickel provided neopentyl alcohol **119** in low yield, a second product being the acetonide-migrated C(5)-alcohol. Although hydrogenation with palladium on carbon led to a similar result, sodium in ammonia accomplished the transformation adequately (84%). In

---

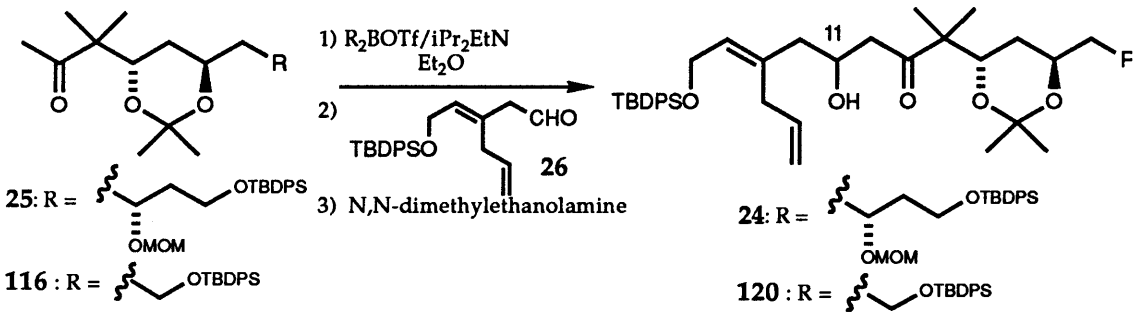
* sodium bis(2-methoxyethoxy)aluminum hydride

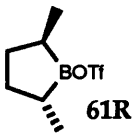
order to avoid reduction of the phenyl groups on silicon, however, it was necessary to use precisely two equivalents of sodium. Interestingly, this problem of acetonide migration during debenzylation was only occasionally observed in the synthesis of fragment A (**25**), and only to a small degree. Swern oxidation of alcohol **119**,[30] followed by treatment of the resulting aldehyde with methyllithium and a second Swern oxidation afforded fragment A' methyl ketone **116** (87%, 3 steps).

7.3 Coupling of Fragments A' and B

Our focus returned to the creation of the C(11)-stereogenic center (Scheme 7-3). One would expect that the coupling of fragment A' (**116**) with fragment B (**26**)

Scheme 7-3



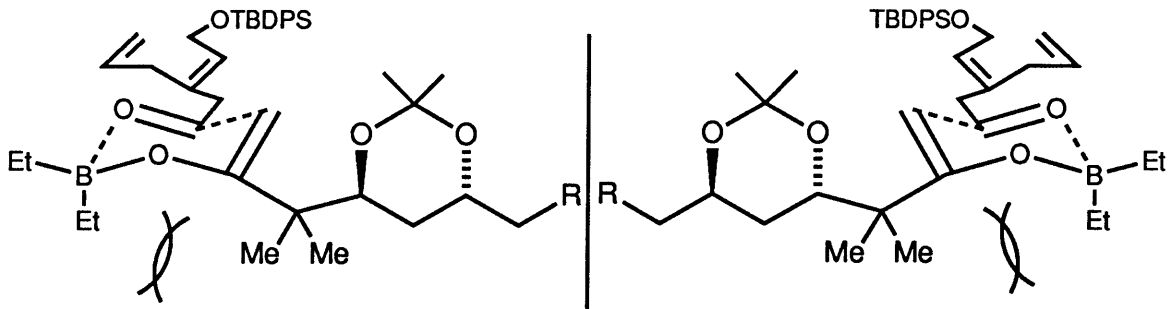
ketone	C(11)*R*/C(11)*S* with Et_2BOTf	C(11)*R*/C(11)*S* with  **61R**
25	2 : 1	6 : 1
116	3 : 1	8 : 1

would lead to a near-identical diastereomeric ratio as that obtained with fragment A (**25**) since the structural difference between these methyl ketones (**25** and **116**) is six carbons away from the presumed Zimmerman-Traxler transition state[59] associated with their reaction (vide infra). Indeed, the diastereoselectivity of **116**, was only slightly different from that of **25**, and, to our satisfaction, even more in favor of the

desired C(11)*S*-diastereomer. Thus, the C(11)*S*/C(11)*R* ratio observed was 3:1 with diethylboryl triflate[45] and 8:1 with **61R**,[21] as indicated by HPLC (ca. 2:1 and 6:1 for **25** with the same boron reagents respectively).

It is appropriate to discuss briefly what can be said about the origin of the above product ratios. The diastereomeric transition states depicted as **121S** and **121R**, which lead to the C(11)*S*- and C(11)*R*-products respectively, are presented below (Figure 7-1). The indicated interaction is presumed be the major controlling element

Figure 7-1



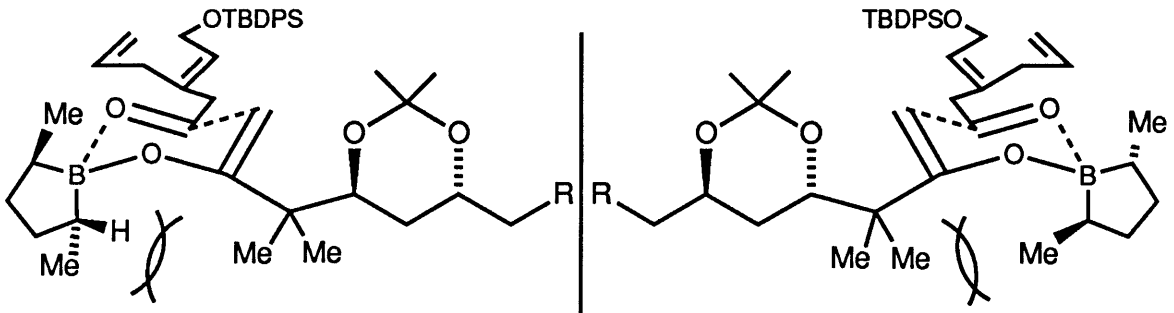
121*S* (transition state leading to 11*S*) **121*R*** (transition state leading to 11*R*)

that results in an energy difference between these transition states (i.e. the D.S. of the aldol reaction).[21] Clearly subtle, and difficult to rationalize, is the effect that the R-group has on the energy difference between **121S** and **121R**. Reiterating the product ratios in terms of the associated transition states, however, we can say that when R is the C(3)-silyloxy group (ketone **116**), **121S** is preferred 3:1 over **121R**, but when R includes the [C(1)-C(2)]-subunit (ketone **25**), the preference is 2:1. This exemplifies the delicate nature of the intrinsic D.S. of fragments that might be used in convergent synthesis. Indeed, we were quite fortunate that the use of our modified ketone (i.e. **116** rather than **25**) in the fragment-coupling reaction did not *reverse* the stereochemical preference to provide the undesired C(11)*R*-**120**. Continuing our consideration of Figure 7-1, we would expected that the asymmetry of the acetonide-protected diol *would* affect the energetic difference between **121S** and **121R** due to a

statistical, conformational bias of the gem-dimethyl group imposed by this asymmetry. Which diastereomeric transition state is preferred, however, is unpredictable.

The only component of this transition state that behaves in a predictable manner is the chiral reagent. Consider the transition states for the double asymmetric reaction in which chiral boron reagent **61R** is utilized (Figure 7-2). The

Figure 7-2



122*S* (H-Me interaction leading 11*S*) **122*R*** (Me-Me interaction leading to 11*R*)

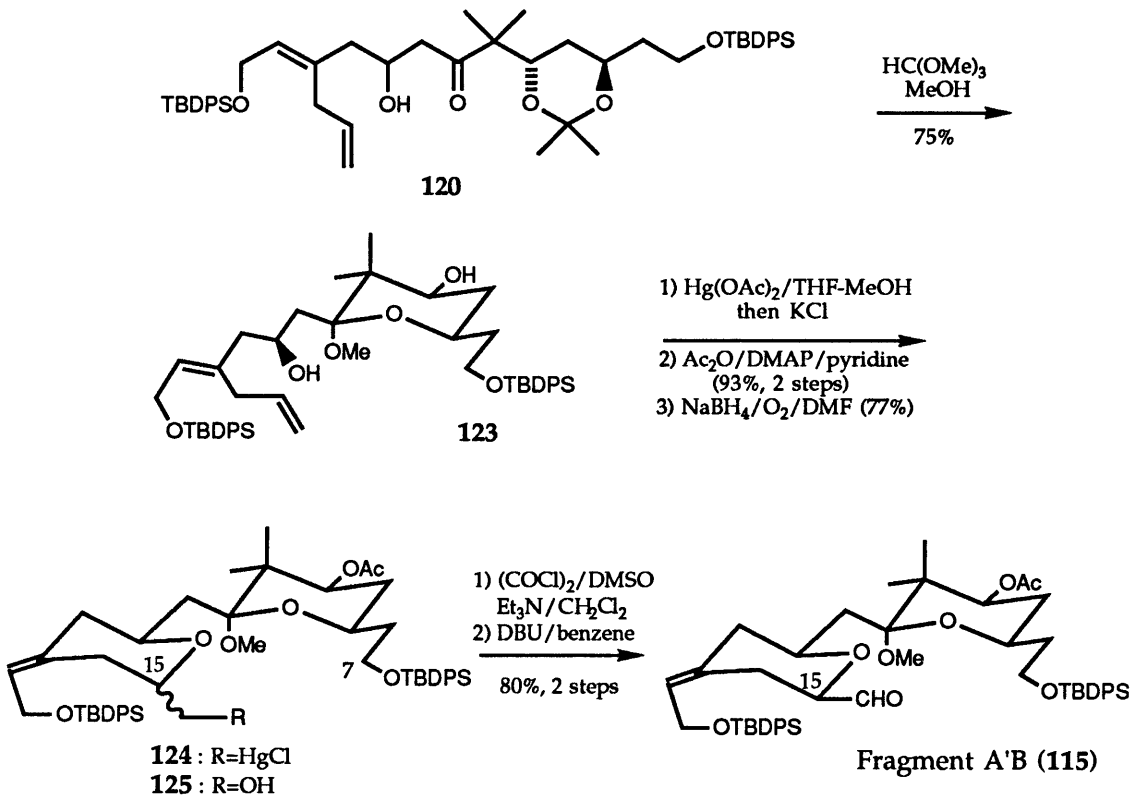
effect of replacing the diethylboryl moiety by the *R,R*-2,5-dimethylborolanyl moiety is expressed unambiguously by this model. The indicated H-Me interaction (in **122*S***), apparently decisive in this reaction, is favored to the Me-Me interaction (in **122*R***). Thus, transition state **122S** is predictably lower in energy and we observe that the C(11)*S*-diastereomer is enhanced by the chiral reagent. Mediation of this reaction by the *S,S*-reagent clearly reverses this preference. In this context, it is apparent that more powerful external chiral reagents would be of great utility.

7.4 Completion of Fragment A'B

Fragment A'B (**115**) was completed with minor modifications to the route developed for its [C(1)-C(16)]-counterpart (see section 4.2). Treatment of β-hydroxy ketone **120** with pyridinium *p*-toluenesulfonate in methanol/trimethyl orthoformate removed the labile acetonide and directly afforded the ring-closed

product **123** as the expected 8 : 1 mixture of separable diastereomers (85%) (Scheme 7-4). Initially, the second pyran-ring forming step was surprisingly inefficient. The

Scheme 7-4



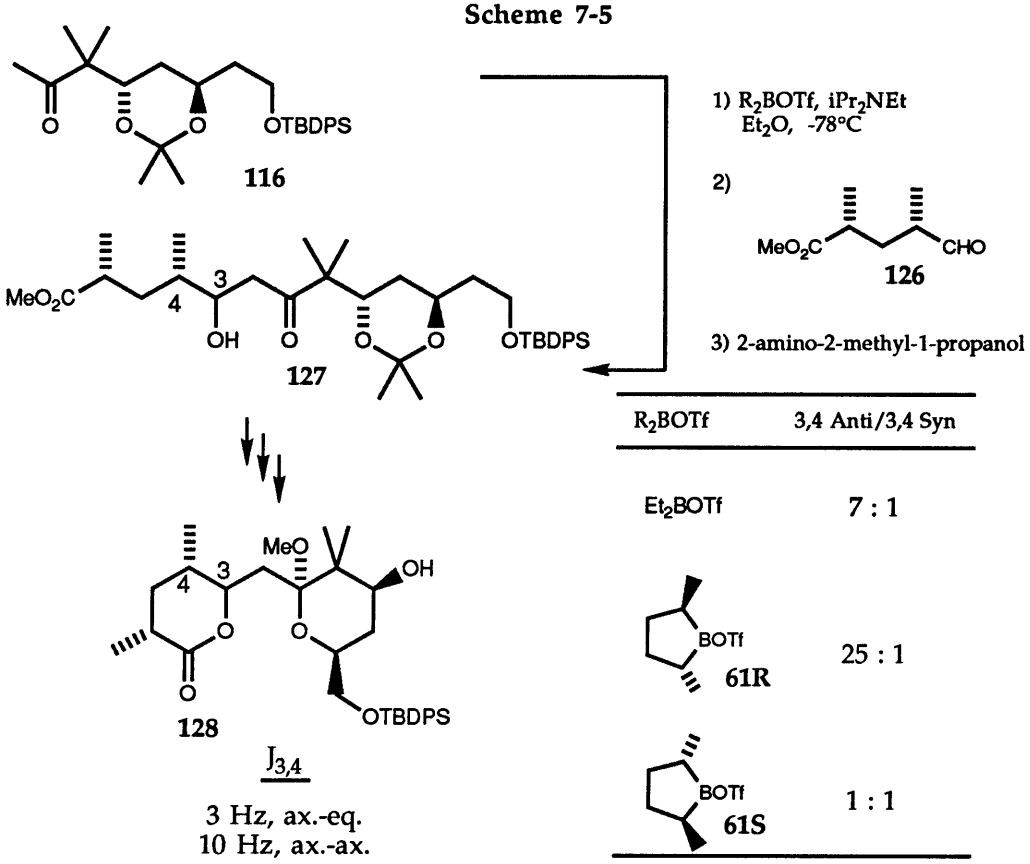
usual rapid addition of mercuric acetate led to several byproducts,[60] presumably arising from a non-selective reaction with both olefinic moieties of **123**. To avoid this complication, the reagent was added portionwise over 2 h and ultimately, cyclization of olefinic alcohol **123** followed by acetylation at O(7) afforded **124** in good yield (93%). Oxidative demercuration with sodium borohydride and molecular oxygen[47] led to alcohol **125** (75-85%). Swern oxidation,[30] followed by stirring the resulting 1 : 1 mixture of C(15)-epimers with aluminum oxide in benzene for 20 h, afforded aldehyde **115** as a 9 : 1 mixture [C(15)*S*/C(15)*R*] on a 75 mg scale. It is noteworthy that when this reaction was initially performed on a preparative scale (1.0 g), a gross mixture of aldehydic products was obtained with the desired aldehyde

isolated in only 10% yield. It was found that 50-70% yields of the C(15)-epimerized product could be achieved on this larger scale by *not* increasing the quantity of aluminum oxide used. Alternatively, a 5:1 mixture of C(15)-epimers could be obtained by use of DBU* in benzene in considerably higher yield (94%).

7.5 Digression : Triple Asymmetric Synthesis (T.A.S.)

We hoped to illustrate that the rule of D.A.S.[25] could be extended to T.A.S. (i.e. the case in which three chiral components participate in a reaction). In collaboration with Drs. Allen Duplantier and Peter Somfai, the reaction of ketone **116** with aldehyde **126**, both of known D.S. (*ca.* 3:1 and 2:1, 3,4-anti

Scheme 7-5



* 1,8-diazabicyclo[5.4.0]undec-7-ene

selective respectively),[61] was examined (Scheme 7-5). As expected for this pair, the double asymmetric aldol reaction mediated by achiral diethylboryl triflate[45] provided the aldol products **127** with a 7:1 ratio of diastereomers (predicted at *ca.* 3x2). That the anti diastereomer was indeed the major product was confirmed by converting the mixture to the pyranyl lactone diastereomers **128**, and measuring the $J_{3,4}$ values.[62] Matched with both **116** and **126** is the chiral reagent **61*R***, the D.S. of which was approximated at 3-4:1 from reactions of *t*-butyl methyl ketone with various achiral aldehydes.[21b] The utilization of this external chiral reagent in the triple asymmetric aldol reaction enhanced the above stereoselection to 25:1 (*ca.* 3x2x3), thus exemplifying the stereoselection achieved in a fully matched system. The matched-mismatched reaction using **61*S***, which led to a 1:1 mixture of the diastereomers (*ca.*3x2/3), demonstrates how selection of reagent chirality may be utilized to enhance formation of either diastereomer.

These predictable product ratios suggested the validity of an approximate multiplicativity rule even for T.A.S. (for an additional example of T.A.S. see Appendix III, third publication). Our results also indicated that reagents with a larger D.S. than those described above will override any opposing substrate preference in mismatched systems, providing absolute stereochemical control, simply through the selection of a proper reagent (as in the case of D.A.S.).

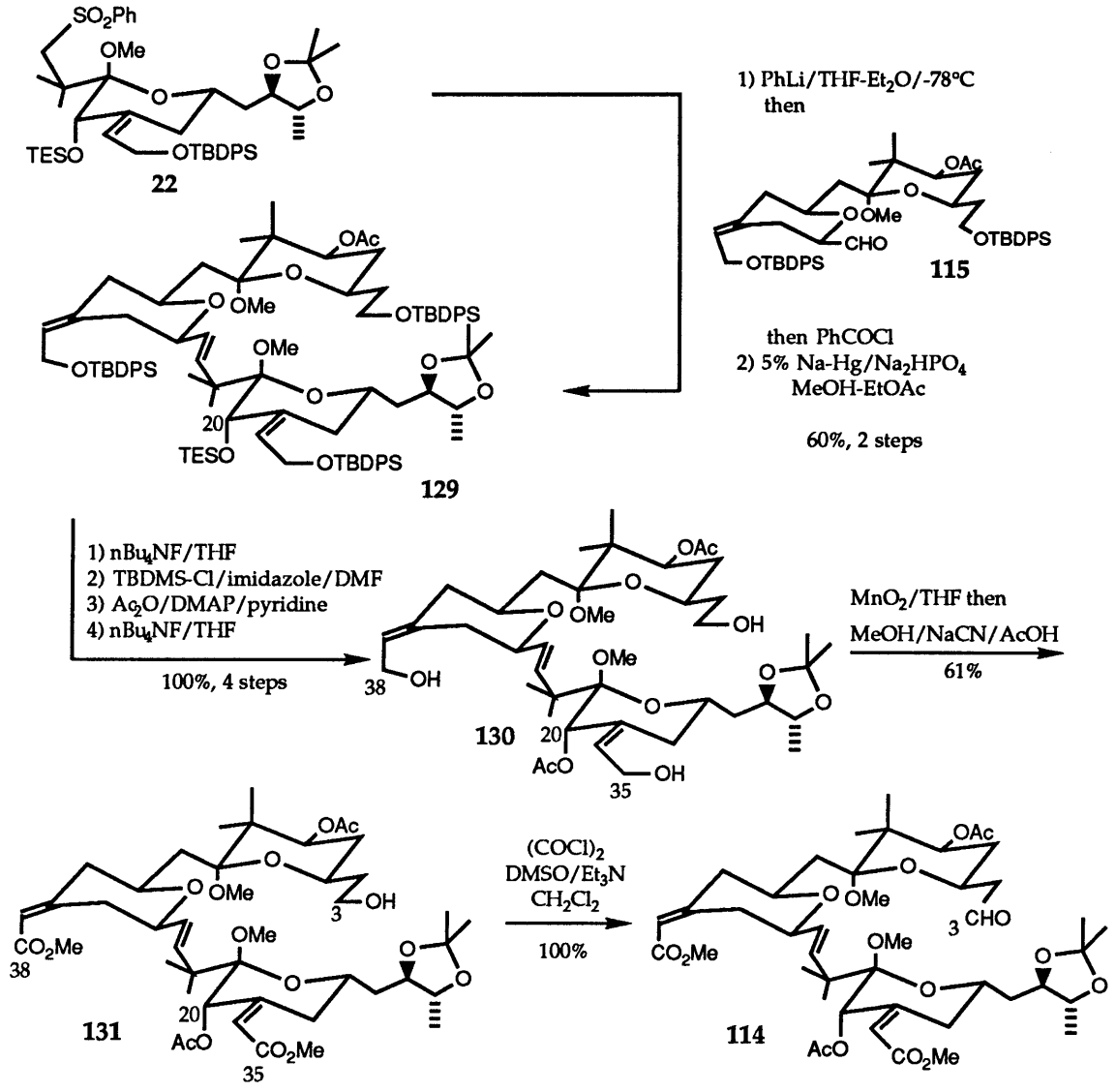
Chapter 8

Final Approach to Bryostatin 7

8.1 Synthesis of a Seco Thioester Derivative

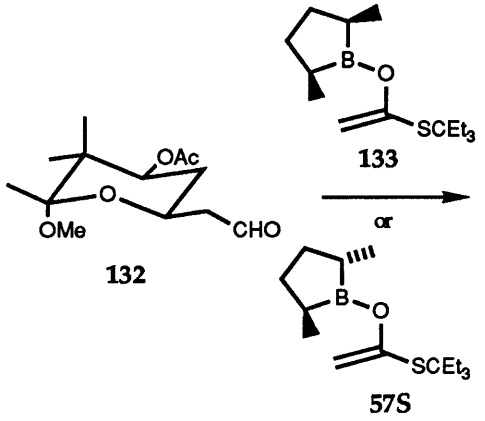
The next step in our synthetic plan involved the Julia-Lithgoe olefination (Scheme 8-1),[20] previously accomplished with fragment CD (**22**) and fragment AB

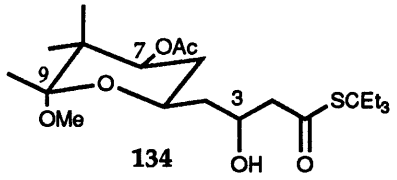
Scheme 8-1



(21) (see section 6.1). Sulfone **22** and fragment A'B (**115**) were supplied by the author. Fortunately, Dr. Kageyama was able to couple these fragments as before. Selective acetylation of **129** at C(20) to provide triol **130** and ester formation at C(35) and C(38) to afford C(3)-alcohol **131** could also be accomplished as before (see section 6.2). Oxidation at C(3) to aldehyde **114** was effected by the Swern protocol.[30]

What remained to complete the framework of the seco acid was incorporation of the [C(1)-C(2)]-subunit. The author's contribution to this aldol step was the execution of a model study (eq 8-1) to determine (i) the expected





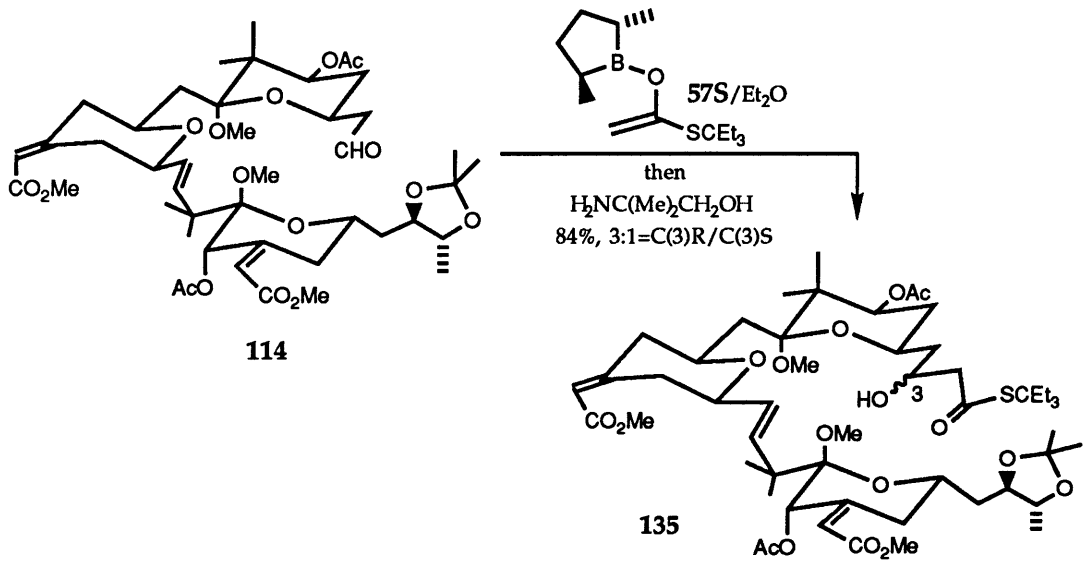
(8-1)

C(3)S/C(3)R with **133**	C(3)S/C(3)R with **57S**
3 : 1	1 : 3

diastereoselectivity and (ii) the ^1H NMR features that might be used to determine this selectivity in the reaction of aldehyde **114** and boron enolate **57S** (see Scheme 8-2). Treatment of model **132** with achiral (meso) boron enolate **133**[21] led to a 3:1 mixture of diastereomers **134**, easily distinguishable by ^1H NMR [baseline resolution at the C(7)-methine (δ 5.62 and 5.50), the C(3)-methine (δ 4.31 and 4.43), and the C(9)-methyl acetal (δ 3.07 and 2.97)]. Use of (*S,S*)-boron enolate **57S**,[21] selective for the desired C(3)*R* stereochemistry, provided a 1:3 mixture of the same diastereomers and thus, based on the rule of D.A.S.,[25] the two sets of resonances, (i) 5.62, 4.31, and 3.07 ppm and (ii) 5.50, 4.43, and 2.97 ppm, could be assigned as C(3)*S* and C(3)*R* respectively. The conclusion, however, was that the remarkable intrinsic selectivity of the chiral aldehyde was for the undesired C(3)*S*-diastereomer. Indeed,

experiments conducted by Dr. Kageyama indicated that the [C(3)-C(27)]-system (aldehyde **114**) behaved identically in its condensation with enolate **57S**, which resulted in a 3:1 mixture of inseparable products (83%) (Scheme 8-2). The major

Scheme 8-2



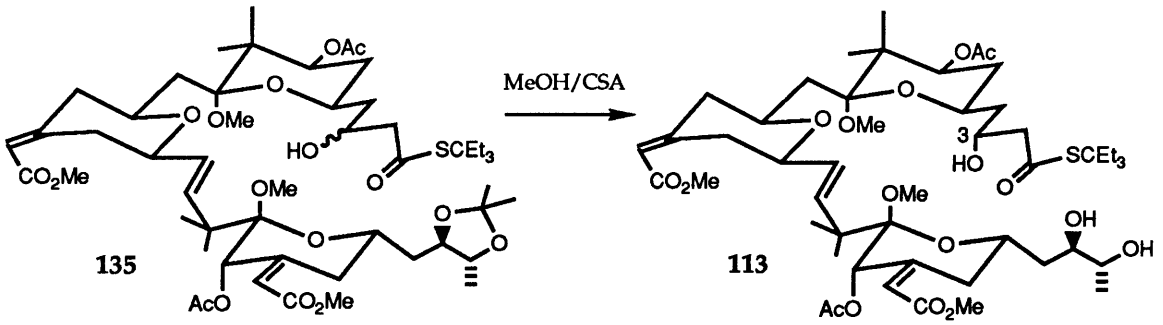
diastereomer from this reaction was tentatively assigned as β-hydroxy thioester C(3)*R*-**135** based on a comparison of the ^{1}H NMR spectra of the model (**134**) and **135**, and this assignment was confirmed at a later stage (vide infra). The ability of the chiral boron enolate to override the inherent selectivity of aldehyde **135** (mismatched case), even to this modest degree, was accepted gratefully. We had finally achieved the synthesis of a C(3)-*unprotected* seco acid derivative.

8.2 Macrolactonization and Final Steps

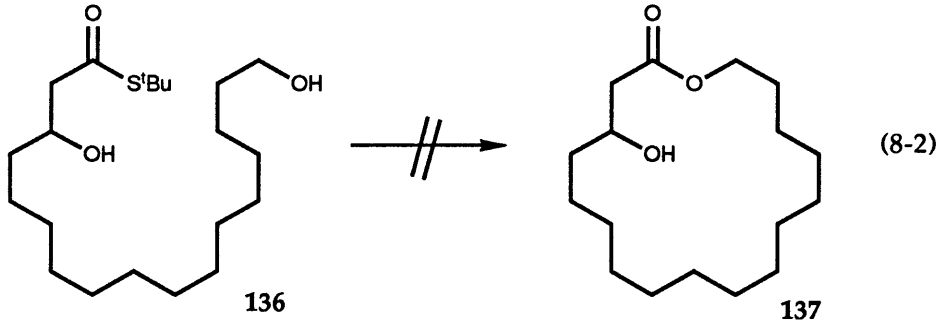
It was necessary to liberate the C(25)-alcohol moiety in preparation for macrolactonization studies. Dr. Kageyama found that seco thioester **135** was relatively acid sensitive, as expected. Unanticipated, however, was the impressive acid resistance exhibited by the O(25)-, O(26)-acetonide moiety which, from a number

of model compounds, had been hydrolyzed under mild conditions (e.g. see eq 6-2). Consequently, the removal of this 1,2-diol protecting group was accompanied by competitive decomposition processes, as indicated by loss of the characteristic olefinic proton resonances in the NMR spectrum. Partial conversion to diol **113** (isolated as a single diastereomer) by treatment of acetonide **135** with camphor sulfonic acid in anhydrous methanol proved to be a relatively efficent process. The recovered **135** (40%) was recycled (Scheme 8-3).

Scheme 8-3



Macrolactonization of seco thioester **113** was the next step in our planned synthetic route. Although some thioester-alcohols have behaved well in such a lactonization,[58] Dr. Kageyama concluded from model studies that β-hydroxy thioesters are not amenable to this method. For example, treatment of **136** (eq 8-2)



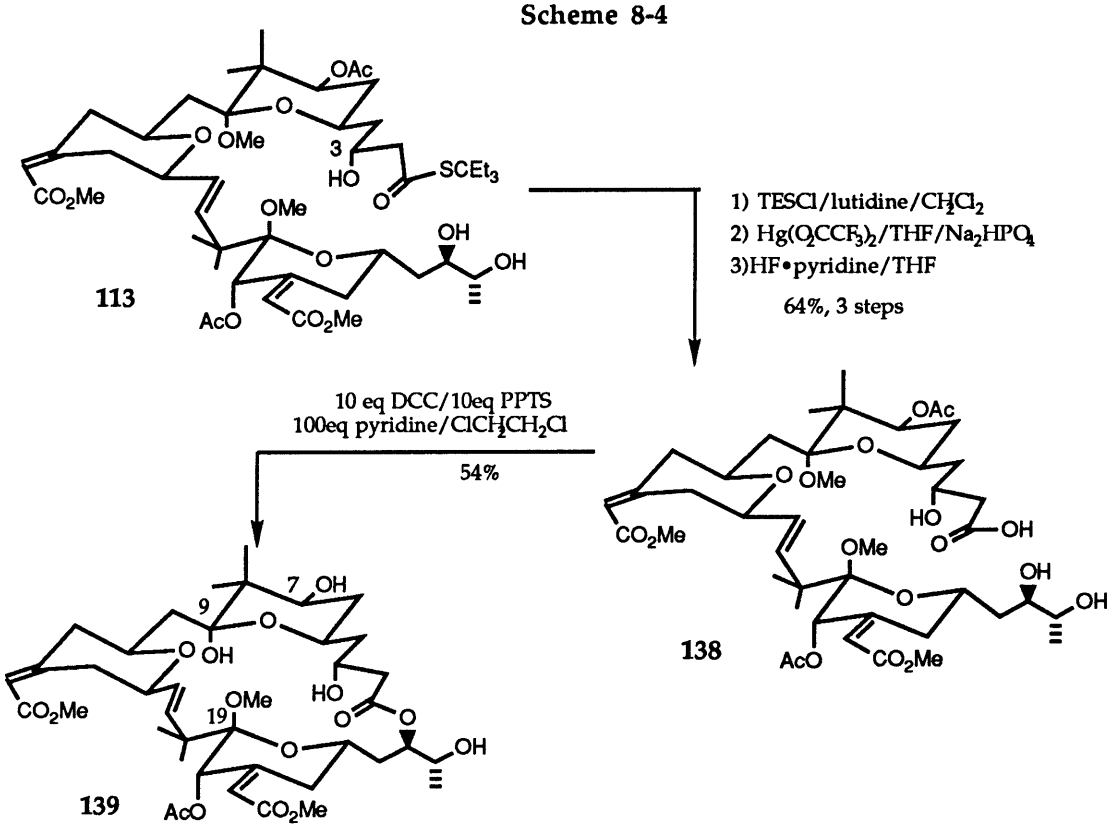
(8-2)

with thiophilic metal cations [e.g. mercuric trifluoroacetate, silver(I) trifluoroacetate, silver(I) perchlorate, and copper(I) triflate] led to no formation of macrolactone **137**

(eq 8-2). Direct macrolactonization of thioester **113** was therefore not pursued.

Dr. Kageyama directed his efforts toward the more commonly utilized macrolactonization substrate: the seco acid. In the conversion of thioester **113** to carboxylic acid **138** by use of mercury(II) (Scheme 8-4), the highest yields were

Scheme 8-4



obtained by blocking possible closure to the β-lactone.[63] Thus, when silylation with excess silyl chloride preceded treatment with mercuric trifluroacetate, and the resulting carboxylic acid was desilylated with hydrofluoric acid/pyridine, seco acid derivative **138** was obtained (64%, 3 steps).

Macrolactonization of seco acid, bismethyl acetal **138** proved challenging. Precedented procedures[15] led to gross decomposition of the bryostatin framework, and no discernable lactone formation. Dr. Kageyama discovered, however, that in

the case of Keck's procedure,[64] which involves DMAP* hydrochloride-catalyzed lactonization with DCC**, the culprit leading to this loss of structural integrity was DMAP hydrochloride. By replacement of DMAP with excess pyridine [ten equivalents of DCC and pyridinium *p*-toluene sulfonate and 100 equivalents of pyridine in refluxing dichloroethane], he obtained a 51% yield of the desired product **139** and approximately 10% of a separable byproduct [presumably the C(26) macrolactone]. The site of macrolactonization in the major product [i.e. O(25) verses O(26)] was unambiguously elucidated by 2D ^{1}H NMR [from the downfield shift of the C(25)-methine proton]. It should be noted that the C(7)-acetate moiety was hydrolyzed during the mildly acidic conditions of macrolactonization and that the relatively labile C(9)-methyl acetal was hydrolyzed during the workup procedure (methanol/acetic acid).

There remained one major problem : hydrolysis of the C(19)-methyl acetal in **139**. From our work with previous systems (see Schemes 5-4 and 6-3), we anticipated that this functionality would exhibit considerable acid resistance. Indeed, conversion of methyl acetal **139** to its corresponding C(19)-hemiacetal could not be achieved directly. Our attention turned to modification of the lower pyran ring of **139**. Most notable, was the likely effect of the acetate withdrawing group adjacent to C(19) where a significant positive charge must form in the transition state of hydrolysis. As part of a plan to deacetylate at C(20) and continue hydrolysis studies, Dr. Kageyama treated **139** with potassium carbonate in methanol. We were astonished to discover that during a mild acidic workup [5% aqueous hydrochloric acid], the desired C(19)-hemiacetal **140** was liberated spontaneously (54%) (Scheme 8-5). A similar observation has be reported by Kishi et al.[65]

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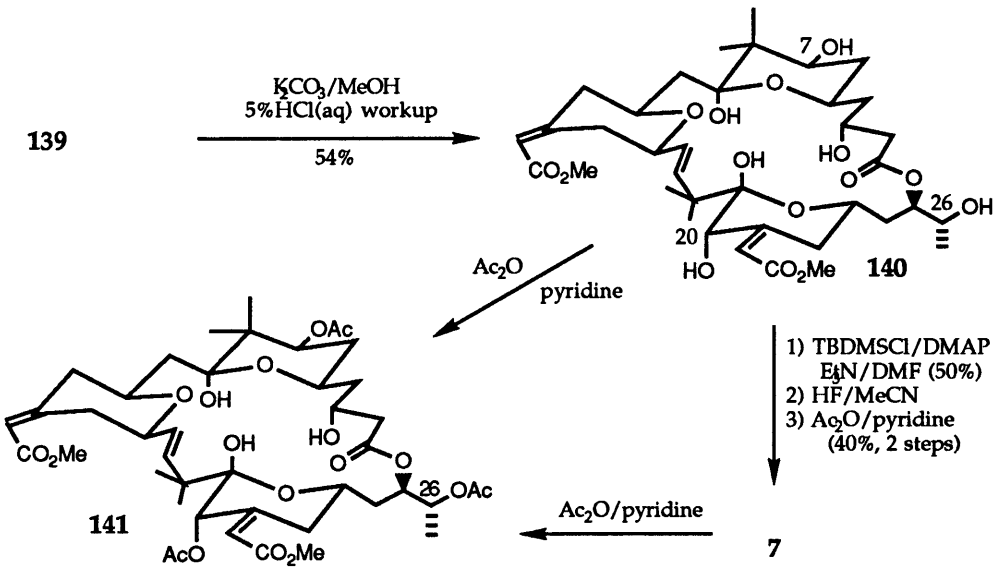
* 4-(dimethylamino)pyridine
** dicyclohexylcarbodiimide

Scheme 8-5



Finally, we had an opportunity to confirm the C(3)*R*-stereochemical assignment, tentatively made by a comparison between the model system in equation 8-1 and the seco thioester in Scheme 8-2. Acetylation at C(7), C(20), and C(26) afforded triacetate **141**, which Dr. Kageyama concluded was identical, as indicated by TLC and ^{1}H NMR, to that prepared from natural **7**.*

What remained in our synthesis of bryostatin **7** was the selective acetylation at O(20) and O(7) in the presence of the C(26)-hydroxyl group. Dr. Kageyama was able to accomplish this task by selective silylation at O(26) with *tert*-butyldiphenyl silyl (TBDPS) chloride, acetylation at O(7) and O(20), and treatment with hydrofluoric acid/pyridine (40% from **140**). The resulting product co-eluted with authentic **7** in several solvent systems, and the ^{1}H NMR spectra of these two samples in d_6-benzene were identical. We had anticipated that the concentration dependence of the ^{1}H NMR spectrum displayed by the natural product would serve well to compare the bryostatin **7** samples of natural and synthetic origin. Indeed, this concentration

* We thank Professor G. R. Pettit and Y. Kamano for their generous supply of samples of bryostatin 1 and 7 and helpful suggestions.

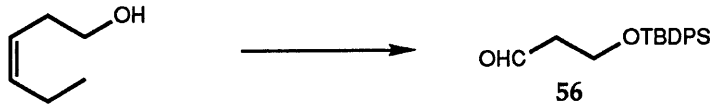
dependence followed the same trend for both samples, thus securing the success of our synthesis.

Chapter 9

Experimentals for Schemes

Reactions were performed in flame-dried glassware under Ar or N_2. Solvents and reagents were purified using standard procedures. Column chromatography was performed with 230-400 mesh silica gel (Merck), and preparative TLC was performed with UNIPLATE thin layer chromatography plates (Analtech). NMR spectra were recorded on a Bruker WM250, Bruker AC250, Varian XL300, Varian VXR500 or Gemini 300 spectrometer. Chemical shifts are reported in ppm (δ) relative to residual solvent resonances. IR spectra were recorded on either a Perkin-Elmer 283B or a Hitachi 270-30 infrared spectrophotometer. Mass spectra were obtained using a Finnigan MAT 8200 spectrometer. Optical rotations were recorded at ambient temperature on an Autopol III or a Perkin-Elmer 124 polarimeter. HPLC analysis was performed on a Waters 6000A instrument equipped with a Chemcosorb 3 Si column (4.6 x 250 mm) and UV detection (254 nm).

Preparation of Aldehyde 56 (Scheme 3-2)



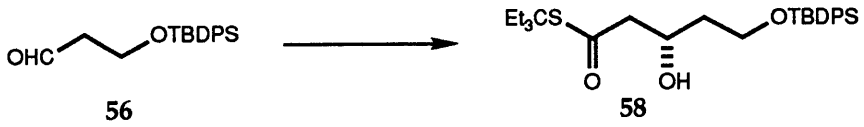
56

A solution of CH_2Cl_2 (50mL), *cis*-3-hexen-1-ol (1.0g, 10mmol), *i*Pr_2EtN (2.7mL, 15mmol), catalytic imidazole, and TBDPS-Cl (2.8mL, 11mmol) was stirred at room temperature for 40 h. The reaction mixture was poured into 3:1 hexane/ethyl acetate (200mL) and washed with saturated $NaHCO_3$(aq), and saturated NaCl(aq). After drying over $MgSO_4$, filtration and concentration in vacuo led to 3.8g of the crude silyl ether which was used directly in the next step without purification. A stirred solution of this silyl ether (3.8g, <10mmol) in 4:1 CH_2Cl_2/MeOH (70mL) was cooled to -78°C and subjected to a steady flow of ozone. When the solution remained blue without additional ozone, dimethylsulfide (3.0mL, 41mmol) was added and the cooling bath was removed. After 30 min, Et_3N (3.0mL, 22mmol) was added and the reaction mixture was heated at reflux for 20 min. Phosphate buffer (200mL, pH 7) was added and the aqueous layer was extracted with 4:1 hexane/ethyl acetate. After drying over $MgSO_4$, filtration, and concentration in vacuo, SiO_2 chromatography (5:1 hexane/ethyl acetate) yielded 2.9g (87%, 2 steps) of **24**.

IR (neat) 3020-2800, 2720, 1740, 1130-1080 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 1.03 (s, 9H), 2.61 (dt, J = 7, 2 Hz, 2H), 4.02 (t, J = 6 Hz, 2H), 7.40 (m, 6H), 7.64 (m, 4H), 9.82 (t, J = 3 Hz, 1H).

Preparation of Thioester 58 [Scheme 3-2 (cont.)]



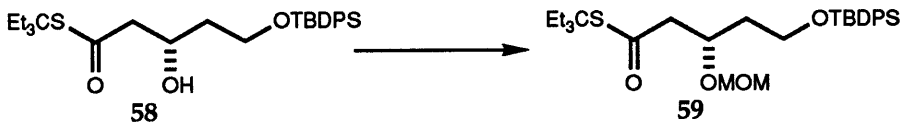
A stirred solution of $Et_3CSC(O)Me$ (87mg, 0.50mmol) in pentane (3.0mL) was cooled to -78°C. After rapid addition of iPr_2EtN (107μL, 0.60mmol), triflate **61R** (127μL, 0.60mmol) was added dropwise. After 30 min the solution was warmed to 0°C, and stirred for 1 h to insure the formation of enolate **57R**. The reaction mixture was cooled to -78°C, and a solution of aldehyde **56** (200mg, 0.65mmol) in pentane (0.4mL) was added dropwise. After 1 h the reaction mixture was warmed to room temperature for 10 min, and subsequently quenched by addition of excess N,N-dimethyl ethanolamine. The mixture was diluted with saturated NH_4Cl (aq), and extracted with ether, washed with saturated NaCl (aq), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by preparative TLC (8:1 hexane/ethyl acetate) gave 191mg of **26** [79%, 89%ee, determined by ^1H NMR analysis of the corresponding Mosher's ester derivative].

IR (neat) 3530-3300, 3000-2810, 1670, 1120-1050 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 0.85 (t, J = 7 Hz, 9H), 1.03 (s, 9H), 1.77 (m, 2H), 1.76 (q, J = 8 Hz, 6H), 2.65 (m, 2H), 3.40 (d, J = 4 Hz, 2H), 3.81 (m, 2H), 4.28 (m, 1H), 7.38 (m, 6H), 7.65 (m, 4H)

HRMS $[M-C_4H_9]^+$ calculated: 429.1919, found: 429.1918

Preparation of Methyoxymethyl Ether 59 [Scheme 3-2 (cont.)]



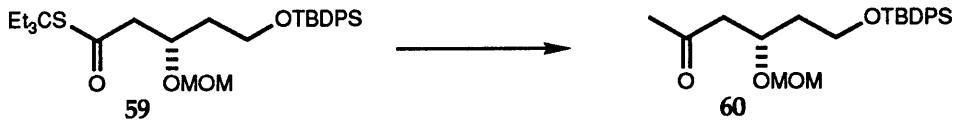
A solution of $(MeO)_2CH_2$ (2.2mL, 24mmol) and **58** (200mg, 0.44mmol) in $CHCl_3$ (3.6mL) at 0°C was added to a slurry of P_2O_5 (1g, 7mmol) in $CHCl_3$ (3.6mL) and stirred at 0°C. After 1.5 h the reaction was complete by TLC and was quenched by addition of saturated Na_2CO_3 (aq), extracted with ether, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude oil was purified by preparative TLC (10:1 hexane/ethyl acetate) to obtain 196mg (91%) of **59**.

IR (neat) 2980-2810, 1670, 1100-1070 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.85 (t, J = 7 Hz, 9H), 1.04 (s, 9H), 1.77 (q, J = 7 Hz, 6H), 1.78 (m, 2H), 2.63 (dd, J = 14, 7 Hz, 1H), 2.77 (dd, J = 14, 7 Hz, 1H), 3.27 (s, 3H), 3.72 (m, 2H), 4.20 (m, 1H), 4.59 (A of AB d, J = 7 Hz, 1H), 4.61 (B of AB, J = 7 Hz, 1H), 7.38 (m, 6H), 7.62 (m, 4H)

MS (m/z) $[M]^+$ 530, 473, 472

Preparation of Ketone 60 [Scheme 3-2 (cont.)]



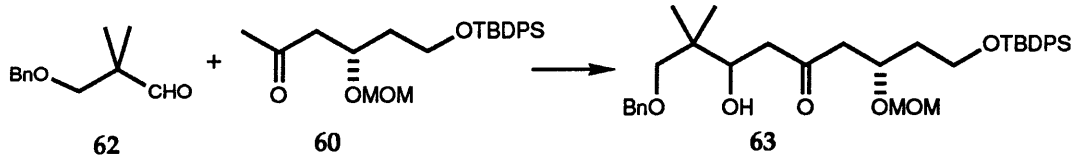
At 0°C, DMS•CuBr (250mg, 1.2mmol) was stirred in ether (5.0mL), and MeLi (1.7M in ether, 1.4mL, 2.4 mmol) was added dropwise. The reaction vessel was cooled to -78°C and a solution of **59** (196mg, 0.37mmol) in ether (0.5mL) was added dropwise. The reaction mixture was warmed -15°C, and stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl (aq) and extracted with ether, and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Preparative TLC (8:1 hexane/ethyl acetate) led to 145mg (94%) of **60**.

IR (neat) 2980-2820, 1710, 1100-1070 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.85 (m, 2H), 2.12 (s, 3H), 2.55 (dd, J = 14, 7 Hz, 1H), 2.74 (dd, J = 14, 7 Hz, 1H), 3.25 (s, 3H), 3.72 (m, 2H), 4.22 (m, 1H), 4.58 (AB apparent singlet, 2H), 7.37 (m, 6H), 7.63 (m, 4H)

HRMS $[M-CH_3]^+$ calculated: 399.1992, found: 399.1989

Preparation of β-Hydroxy Ketone 63 [Scheme 3-2 (cont.)]



62 60 63

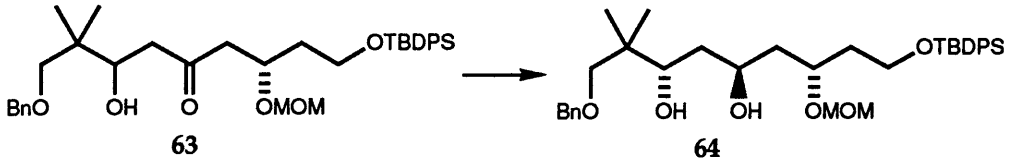
A solution of **60** (119mg, 0.29mmol) in ether (2.5mL) and pentane (2.5mL), was stirred at -78°C. Rapid addition of *i*Pr_2EtN (0.20mL, 0.66mmol) was followed by dropwise addition of **61S** (73μL, 0.33mmol). After 2 h, a solution of aldehyde **62** (66mg, 0.35mmol) in pentane (0.5mL) was added dropwise. After an additional hour the reaction was quenched by addition of excess N,N-dimethylethanolamine, warmed to 0°C, and diluted with saturated NH_4Cl (aq). The organic layer was separated and the aqueous layer was extracted with ether. The combined organics were washed with saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. After preparative TLC (6:1 hexane/ethyl acetate), 152mg (87%) of **63** was obtained.

IR (neat) 3800-3300, 2990-2840, 1720, 1100-1070 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.94 (s, 3H), 1.07 (s, 9H), 1.79 (m, 2H), 2.52 (m, 1H), 2.60 (dd, J = 15, 6 Hz, 1H), 2.80 (dd, J = 15, 7 Hz, 1H), 3.28 (s, 3H), 3.29 (m, 1H), 3.42 (d, J = 5 Hz, 1H), 3.74 (m, 2H), 4.02 (m, 1H), 4.30 (m, 1H), 4.51 (s, 2H), 4.60 (m, 2H), 7.33 (m, 5H), 7.40 (m, 6H), 7.66 (m, 4H)

HRMS $[M-C_4H_9]^+$ calculated : 549.2672, found : 549.2669

Preparation of Diol 64 [Scheme 3-2 (cont.)]



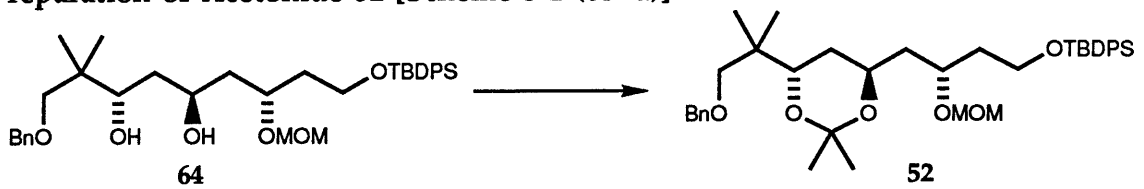
63 64

To a solution of **63** (108mg, 0.18mmol) in MeCN (1.0mL) at -78°C was added a solution of $Me_4NB(OAc)_3H$ (230mg, 0.90mmol) in 1:1 MeCN/AcOH (2.0mL). The reaction was maintained at -20°C and stirred for 38 h. The mixture was diluted with ether and quenched with solid $NaHCO_3$. The organics were washed with saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (2:1 hexane/ethyl acetate) led to 77mg of a major product and 16mg of a minor product (86% combined).

^{1}H NMR (250MHz, $CDCl_3$) (Where the chemical shift differs in the minor diastereomer it appears in [ ]) δ 0.92 [0.84] (s, 3H), 0.94 [0.90] (s, 3H), 1.06 [1.07] (s, 9H), 1.2-1.7 (m, 6H), 3.36 (m, 2H), 3.38 [3.32] (s, 3H), 3.45 [3.50] (OH, 1H), 3.53 [3.62] (OH,1H), 3.76 (m, 2H), 3.83 (m, 1H), 4.07 (m, 1H), 4.18 (m, 1H), 4.48 (A of AB d, J = 8 Hz, 1H), 4.51 (B of AB d, J = 8 Hz, 1H), 4.63 (d, J = 6 Hz, 1H), 4.69 (d, J = 6 Hz, 1H), 7.32 (m, 5H), 7.40 (m, 6H), 7.67 (m, 4H)

HRMS $[M-C_4H_9]^+$ calculated : 551.2828, found : 551.2830

Preparation of Acetonide 52 [Scheme 3-2 (cont.)]



To a solution of diol **64** (5*R*, 7*S*) (72mg, 0.12mmol) in CH_2Cl_2 (1.0mL) was added $(MeO)_2CMe_2$ (12μL, 0.10mmol) and catalytic PPTS (2mg). After 1.5 h the reaction was complete by TLC, and the mixture was diluted with ether. The organics were washed with saturated $CuSO_4$ (aq), water, saturated $NaHCO_3$ (aq), and saturated NaCl (aq), and dried over $MgSO_4$, filtered and concentrated in vacuo. Preparative TLC (20:1 hexane/ethyl acetate) led to 72mg (98%) of **52**, identical with authentic **52** as indicated by the data provided below.

$[\alpha]_D^{24}$ -12.75 (c 0.80, $CHCl_3$)

IR (neat) 3068, 2960, 2860, 1470, 1430, 1380, 1220, 1100, 1035, 910, 815, 720, 690 cm^{-1}

^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.89 (s, 3H), 1.04 (s, 9H), 1.28 (s, 3H), 1.29 (s, 3H), 1.30 (m, 2H), 1.6 (m, 2H), 1.8 (m, 2H), 3.14 (d, J = 8.5 Hz, 1H), 3.3 (m, 4H), 3.35 (d, J = 6.8 Hz, 1H), 3.7-3.85 (m, 4H), 4.45 (m, 2H), 4.65 (m, 2H), 7.3-7.45 (m, 11H), 7.7 (m, 4H)

MS (m/z) $[M-CH_3]^+$ 633, 255, 199, 91, 45

Preparation of Alcohol 71 (Scheme 4-1)

71

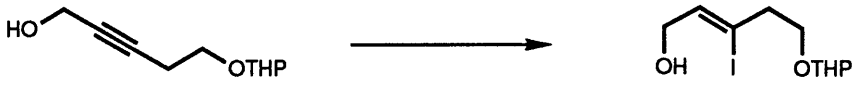
To a solution of 3-butyn-1-ol (3.1g, 30mmol) and DHP (2.4g, 29mmol) in CH_2Cl_2 (50mL) was added catalytic PPTS (10mg). After 3 h, the reaction was complete by TLC, and the reaction mixture was diluted with ether and washed with half-saturated NaCl (aq). The aqueous washes were back-extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Short path distillation (79-82°C, 14mm) afforded 4.8g (89%) of **70**. To a solution of **70** (4.8g, 31mmol) in THF (100mL) at -78°C, was added *n*-BuLi (1.4M solution in hexanes, 25ml, 36mmol) dropwise. After 1 h at -30°C, gaseous formaldehyde was bubbled through the solution for 30 min. The reaction mixture was quenched with saturated NH_4Cl (aq), and diluted with ether. The organic layer was separated, washed with saturated NaCl (aq), and concentrated in vacuo. Purification by SiO_2 chromatography (2:1 hexane/ethyl acetate) led to 4.9g (89%) of **71**.

IR (neat) 3520-3200, 2920-2810, 2210 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 1.4-2.0 (m, 6H), 2.50 (tt, J = 7, 3 Hz, 2H), 3.50 (m, 2H), 3.82 (m, 2H), 4.22 (t, J = 2 Hz, 2H), 4.61 (t, J = 5 Hz, 1H)

HRMS $[M-H]^+$ calculated : 183.1021, found : 183.1021

Preparation of Iodide 72 [Scheme 4-1 (cont.)]



71 72

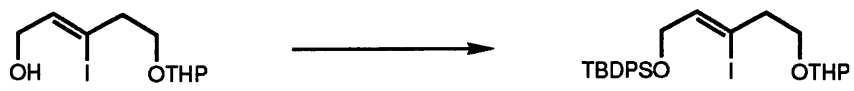
To ether (600mL) was added Redal (3.4M in toluene, 77ml, 272mmol). To this mechanically stirred solution maintained at 0°C was added **71** a solution of (25g, 136mmol) in ether (50mL) dropwise. After 1 h at room temperature, the reaction mixture was cooled to 0°C, and quenched by addition of ethyl acetate (13mL, 133mmol). After cooling to -78°C, iodine (50g, 197mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by slow addition of saturated Na_2SO_3 (aq) and the organic layer was separated and successively washed with Na_2SO_3 (aq), water, and saturated NaCl(aq). The resulting organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (2:1 hexane/ethyl acetate) gave 39.5g (94%) of **72**.

IR (neat) 3510-3180, 2980-2820 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 1.4-1.8 (m, 6H), 2.79 (dt, J = 6, 2 Hz, 2H), 3.51 (m, 2H), 3.83 (m, 2H), 4.20 (t, J = 6 Hz, 2H), 4.66 (t, J = 2 Hz, 1H), 5.95 (t, J = 5 Hz, 1H)

MS (m/z) $[M]^+$ 312, 185, 85

Preparation of Silyl Ether 73 [Scheme 4-1 (cont.)]



72 73

To a solution of **72** (12.0g, 38.5mmol) and imidazole (5.54g, 82.0mmol) in DMF (150mL) at 0°C was added TBDPS-Cl (10.5mL, 40.5mmol). After stirring for 30 min at 0°C and 5 min at room temperature, the reaction mixture was quenched with saturated NH_4Cl (aq), extracted with ether, and washed with saturated NaCl (aq). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 21g (crude weight) of **73** which was used in the next step without further purification. A small sample was purified by SiO_2 chromatography (12:1 hexane/ethyl acetate) for analytical purposes.

IR (neat) 3100-2830, 1160-1020 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.4-1.8 (m, 6H), 2.73 (dt, J = 2, 6 Hz, 2H), 3.49 (m, 2H), 3.80 (m, 2H), 4.22 (dd, J = 2, 4 Hz, 2H), 4.59 (t, J = 4 Hz, 1H), 5.94 (t, J = 5 Hz, 1H), 7.38 (m, 6H), 7.65 (m, 4H)

Preparation of Bisolefin 74 [Scheme 4-1 (cont.)]

73 **74**

To a solution of **73** (21g, 38mmol) in THF (100mL) at -78°C was added CuI (0.43g, 2.3mmol) and then allyl magnesium bromide (1.0M ether solution, 53mL, 53mmol) dropwise. The mixture was allowed to warm to 0°C over 2 h, was stirred for an additional 2 h, and was quenched with saturated NH_4Cl(aq). The mixture was extracted with ether, and the combined organics were washed with saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (12:1 hexane/ethyl acetate) led to 14.6g (82%, 2 steps) of **74**.

IR (neat) 3080-2780, 1630, 1120-1000, 900 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 1.04 (s 9H), 1.4-1.7 (m, 6H), 2.30 (dt, J = 7, 2 Hz, 2H), 2.63 (d, J = 7 Hz, 2H), 3.46 (m, 2H), 3.83 (m, 2H), 4.23 (d, J = 6 Hz, 2H), 4.60 (t, J = 4 Hz, 1H), 4.92 (m, 2H), 5.54 (m, 2H), 7.40 (m, 6H), 7.68 (m, 4H)

HRMS $[M-C_4H_9]^+$ calculated : 407.2042, found : 407.2044

Preparation of Alcohol 75 [Scheme 4-1 (cont.)]

74 **75**

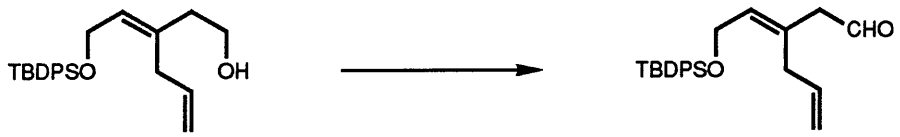
To a solution of **74** (14.6g, 31.5mmol) in ethanol (100mL) was added PPTS (0.95g, 3.8mmol) and the mixture was maintained at 50°C for 2 h. After cooling to ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ (aq), and the ethanol was removed in vacuo. The resulting cloudy solution was diluted with ether, and the aqueous layer was removed. The ethereal solution was washed with saturated NaCl (aq), dried over $MgSO_4$, and concentrated in vacuo. Purification by SiO_2 chromatography (4:1 hexane/ethyl acetate) led to 11.0g (92%) of **75**.

IR (neat) 3580-3200, 3080-2800, 1630, 1120-1000, 900 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.42 (br. s, 1H), 2.24 (dt, J = 6, 2 Hz, 2H), 2.61 (d, J = 6 Hz, 2H), 3.64 (t, J = 6 Hz, 2H), 4.26 (d, J = 6 Hz, 2H), 4.93 (m, 2H), 5.58 (m, 2H), 7.41 (m, 6H), 7.68 (m, 4H)

HRMS $[M-C_4H_9]^+$ calculated : 323.1468, found : 323.1465

Preparation of Fragment B (26) [Scheme 4-1 (cont.)]



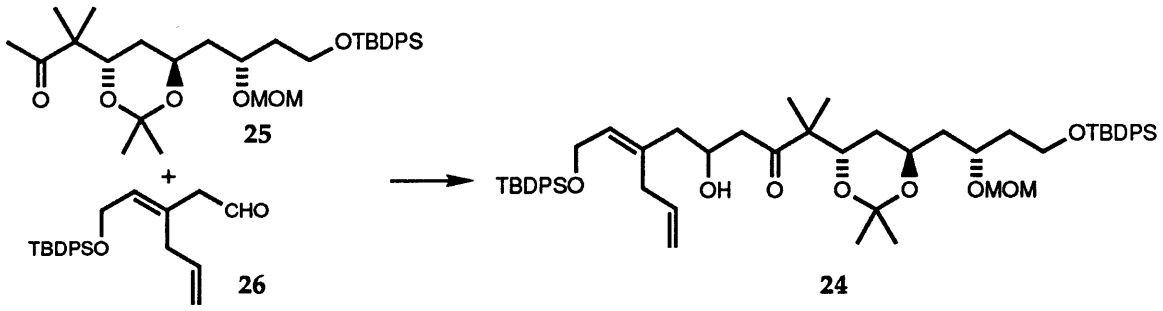
75 **26**

To a solution of pyridine (6.6mL, 82mmol) in CH_2Cl_2 (100mL) at 0°C was added CrO_3 (4.1g, 41mmol) in one portion. After stirring for 15 min at room temperature, a solution of **75** (2.4g, 6.3mmol) in CH_2Cl_2 (10mL) was rapidly added. The mixture was stirred for 15 min at room temperature, diluted with ether, washed with 5% NaOH (aq), 5% HCl (aq), water, and saturated $NaHCO_3$ (aq). The ethereal solution was dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting 2.4g of crude **75** (>95% purity by ^1H NMR) was used in the next reaction without further purification (substantial decomposition was shown to occur on SiO_2 chromatography).

IR (neat) 3060-2800, 2730-2660, 1710, 1630, 1100-1000 cm^{-1}

^1H NMR (300MHz, C_6D_6) δ 1.03 (s, 9H), 2.62 (d, J = 6 Hz, 2H), 3.01 (d, J = 2 Hz, 2H), 4.26 (d, J = 6 Hz, 2H), 4.93 (m, 2H), 5.56 (m, 2H), 7.40 (m, 6H), 7.68 (m, 6H), 9.54 (t, J = 2 Hz, 1H)

Preparation of β-Hydroxy Ketone 24 (Scheme 4-2)



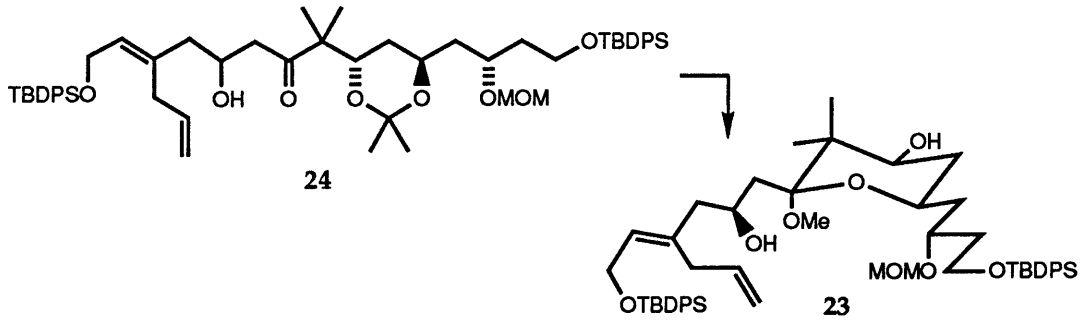
To a solution of **25** (500mg, 0.90 mmol) in ether (15 mL) at -78°C was added *i*-Pr_2EtN (0.62mL, 3.6mmol) followed by the dropwise addition of **61R** (225mg, 0.90mmol). After stirring for 30 min, a solution of **26** (azeotroped with toluene, 500mg, 1.3 mmol) in ether (2 mL) was added and the resultant solution was stirred an additional hour at -78°C. The reaction was quenched by addition of excess N,N-dimethyl ethanolamine, and warmed to 0°C. After recovery of the borolanyl amino alcohol complex by simple filtration, the filtrate was diluted with saturated NH_4Cl (aq) and ether. The organic layer was washed with saturated NH_4Cl (aq) and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash SiO_2 chromatography (4:1 hexane/ethyl acetate) yielded 718mg of (82%) of **24.**

IR (neat) 3080-2800, 1695, 1420, 1130-1000 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 1.05 (s, 21H), 1.12 (s, 3H), 1.28 (s, 6H), 1.3-1.9 (m, 8H), 2.15 (m, J = 7 Hz, 2H), 2.63 (m, 3H), 3.00 [2.95 : minor diastereomer] (d, J = 2Hz, 1H) 3.30 (s, 3H), 3.7-4.0 (m, 6H), 4.13 (m, 1H), 4.23 (d, J = 5.9 Hz, 2H), 4.60 (A of AB d, J = 6.6 Hz, 1H), 4.63 (B of AB d, J = 6.7 Hz, 1H), 4.92 (m, 2H), 5.57 (m, 2H), 7.39 (m, 12H), 7.67 (m, 8H)

MS (m/z) $[M-CH_3]^+$ 933, 889, 872, 833, 801

Preparation of Methyl Acetal 23 [Scheme 4-2 (cont.)]



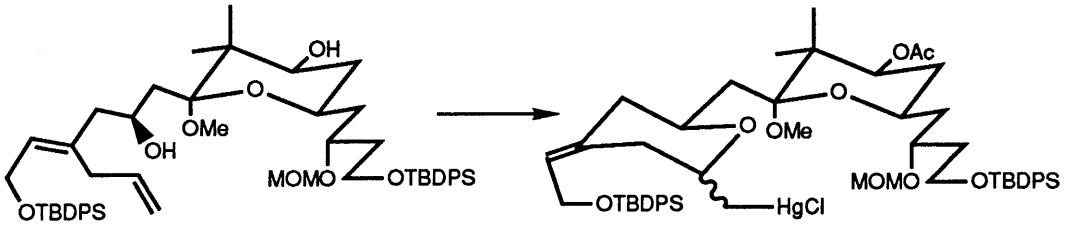
To a stirred solution of **24** (963mg, 1.06mmol) in methanol (16mL) and $(MeO)_3CH$ (2.3mL) was added PPTS (25mg, 0.10mmol). After stirring for 2.5 h at ambient temperature, the mixture was quenched with saturated $NaHCO_3$ (aq), extracted with ether, and washed with water and saturated NaCl (aq). The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Analysis of the crude mixture (^1H NMR) revealed a 6:1 ratio of diastereomers. Flash SiO_2 chromatography (5:1 hexane/ethyl acetate) yielded 143mg of the minor diastereomer [C(11)-epi **23**] contaminated with **23**, and 638mg of diastereomerically pure **23** (85% combined).

IR (neat) 3600-3220, 3040-2810, 2220, 1700, 1140, 1000, 900, 810 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) (when data from the minor diastereomer differs, it appears in [ ]) δ 0.89 (s, 3H), 0.98 (s, 3H), 1.04 (s, 18H), 1.2-1.9 (m, 6H), 2.03 (dd, J = 13, 6 Hz, 1H), 2.28 [2.23] (dd, J=13, 6 Hz, 1H), 2.66 [2.67] (m, 1H), 3.21 [3.20] (s, 3H), 3.29 [3.30] (s, 3H), 3.55 (br. s., 1H), 3.75 (t, J = 6.2 Hz, 2H), 3.83 (m, 1H), 3.91 (m, 1H), 4.02 (m, 1H), 4.17 [4.22] (m, 1H), 4.22 (d, J = 6 [7] Hz, 2H), 4.60 (A of AB d, J = 6.4 Hz, 1H),4.62 (B of AB, J = 6.2 Hz, 1H), 4.91 (m, 2H), 5.57 (m, 2H), 7.38 (m, 12H), 7.67 (m, 8H)

MS (m/z) $[M\text{-}CH_3OH]^+$ 891, 877, 874, 873, 872, 835, 834, 833

Preparation of Organomercurial Chloride 80 (Scheme 4-3)



23 80

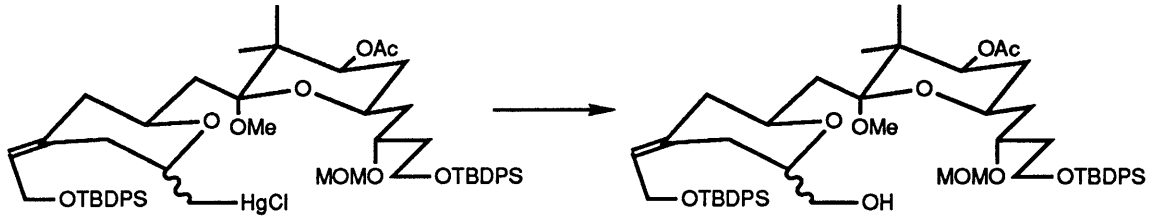
To a solution of **23** (633mg, 0.69mmol) in THF (6.9mL) and methanol (1.7mL) at room temperature was added portionwise $Hg(OAc)_2$ (264mg, 0.83mmol). The colorless solution was stirred for 5 h and was quenched by addition of saturated KCl (aq). After stirring for an additional 30 min, water (4mL) was added and the resultant mixture was extracted with ether. The combined organic extract was washed with saturated $NaHCO_3$ (aq) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo to afford the crude product which was immediately acetylated with AcCl (0.254mL, 3.45mmol) in CH_2Cl_2 (17mL) and pyridine (0.86mL), stirred at 0°C for 2 h. The reaction was quenched by addition of water and the products were extracted with ether. The combined organic extract was washed with saturated $CuSO_4$ (aq), water, saturated NaCl (aq), and dried over $MgSO_4$. Filtration and concentration in vacuo followed by SiO_2 chromatography (4:1 hexane/ethyl acetate) yielded 694mg (84%) of **80** as a white foam.

IR (CH_2Cl_2) 3020-2800, 1735, 1700, 1230, 1110-980 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.04 (s, 21H), 1.16-2.33 (m, 12H), 2.03 (s, 3H), 3.13 + 3.17 (s, 3H), 3.28 + 3.30 (s, 3H), 3.30 + 3.54 (m, 1H), 3.76 (m, 4H), 3.87 (m, 2H), 4.18 (m, 3H), 4.59 + 4.61 (AB apparent singlets, 2H), 5.17 + 5.22 (m, 1H), 5.40 + 5.48 (t, J = 7 Hz, 1H), 7.43 (m, 12H), 7.68 (m, 8H)

MS (m/z) $[M-CH_3O]^+$ 1168, 1148, 1145, 1141, 1111, 1061

Preparation of Alcohol 81 [Scheme 4-3 (cont.)]



80 **81**

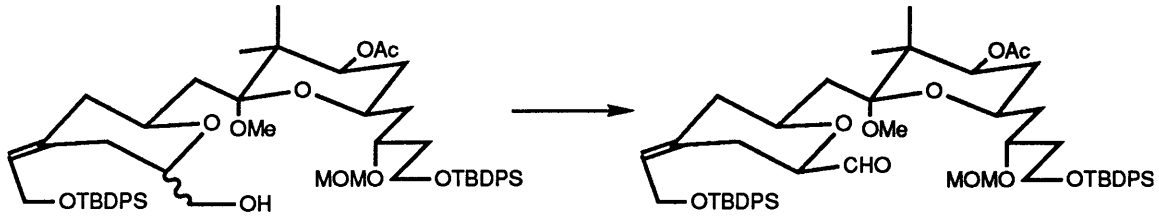
Through a solution of **80** (552mg, 0.46mmol) in CH_2Cl_2 (13mL) was passed a steady stream of O_2 for 10 min from a compressed gas cylinder via a glass capillary tube (solution volume was maintained at >10mL by replacing evaporated CH_2Cl_2). In a separate vessel, a slurry of $NaBH_4$ (160mg, 4mmol) was stirred in DMF (4 mL) and flushed with oxygen in a similar manner for 2-3 min. The borohydride solution was then slowly added to the organomercural chloride solution, via cannula, over a period of 5 min. Oxygen was passed through the reaction mixture for the next 1-2 h and the reaction mixture was quenched by addition of saturated NH_4Cl (aq). The resulting mixture was extracted with ether and the combined organics were washed with water, saturated $NaHCO_3$ (aq), and dried over $MgSO_4$. After filtration and concentration in vacuo, the crude product was purified by flash SiO_2 chromatography (5:1 hexane/ethyl acetate) to provide 365mg (81%) of **81** as a 1:1 mixture of diastereomers.

IR (CH_2Cl_2) 3600-3240, 3040-2810, 1740, 1700, 1140, 1000 cm^{-1}

^{1}H NMR (250MHz, $CDCl_3$) δ 0.92 + 0.94 (s, 3H), 1.04 (s, 21H), 1.2-2.3 (m, 10H), 2.03 + 2.04 (s, 3H), 3.14 + 3.18 (s, 3H), 3.29 (s, 3H), 3.3-3.6 (m, 2H), 3.64 + 4.09 (m, 1H), 3.73 (m, 3H), 3.90 (m, 1H), 4.19 (m, 2H), 4.60 (AB apparent singlet, 2H), 5.19 (m, 1H), 5.44 + 5.47 (t, J = 7Hz, 1H), 7.35-7.42 (m, 12H), 7.66 (m, 8H)

MS (m/z) $[M-CH_3OCH_2]^+$ 919, 917, 891, 859, 857, 769, 635

Preparation of Fragment AB (21) [Scheme 4-3 (cont.)]

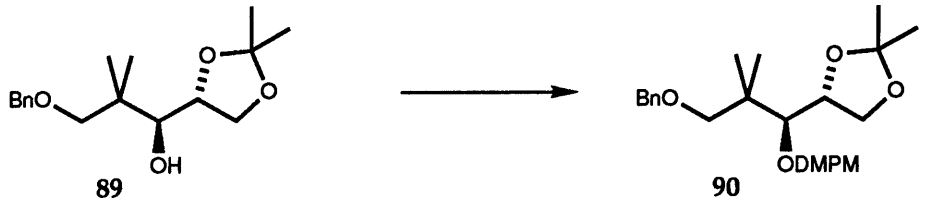


81 **21**

To a solution of $(COCl)_2$ (32μL, 0.37mmol) in CH_2Cl_2 (3mL) at -78°C was added DMSO (52μL, 0.74mmol). After 5 min, a solution of **81** (180mg, 0.18mmol) in CH_2Cl_2 (1mL) was added dropwise. After an additional 30 min at -78°C, Et_3N (136μL, 0.90mmol) was added dropwise, and the mixture was warmed to ambient temperature, stirred for 30 min, and diluted with ether. The organic mixture was washed with 10% HCl (aq), water, and saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude **21**, which hydrates readily, was azeotroped with toluene and subjected to epimerization without further purification. To a solution of dried aldehyde (180mg, 0.18mmol) in benzene (9mL) was added active Al_2O_3 [Woelm® B, 3% water (Act. II), 1.8g]. The resulting slurry was stirred for 20 h at ambient temperature, filtered through Celite (washing with CH_2Cl_2 and ether) and concentrated in vacuo to yield 130mg (74%) of **21** [9:1 C(15)*R*/C(15)*S* by ^1H NMR].

^1H NMR (250MHz, $CDCl_3$) (when data from the minor diastereomer differs, it appears in [ ]) δ 0.94 [0.93] (s, 3H), 1.03 (s, 21H), 2.04 [2.05] (s, 3H), 1.62-2.12 (m, 8H), 2.27 (d, J = 16 Hz, 1H), 2.43 (d, J = 16 Hz, 1H), 3.16 (m, 1H), 3.19 (s, 3H), 3.28 (s, 3H), 3.44 (dd, J = 11, 2.7 Hz, 1H), 3.58 (m, 1H), 3.75 (t, J = 6.0 Hz, 2H), 3.91 (m, 1H), 4.21 (d, J = 6.6 Hz, 2H), 4.59 (AB apparent singlet, 2H), 5.19 (dd, J = 16, 5.4 Hz, 1H), 5.47 [5.43] (t, J = 6.6Hz, 1H), 7.62-7.65 (m, 12H), 7.67 (m, 8H), 9.53 [9.62] (s, 1H)

Preparation of DMPM-Ether 90 (Scheme 5-1)



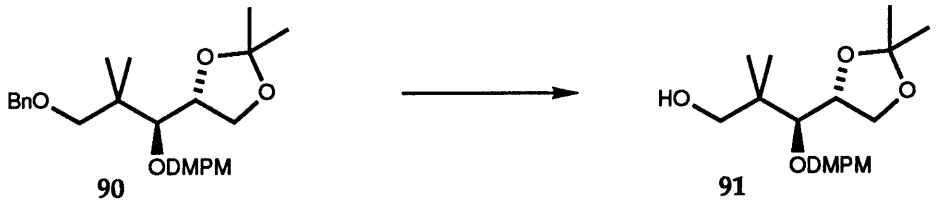
To a slurry of NaH (80% dispersion in mineral oil, 1.2 g, 30 mmol) in DMF (18 mL), stirred at 0°C, was added a solution of **89** (2.9 g, 10 mmol) in DMF (10 mL). After stirring for 30 min, DMPM-Cl (2.8 g, 15 mmol) was added portionwise. After 4 h, the reaction mixture was quenched with methanol (2 mL) and stirred for an additional 20 min. After dilution with saturated NH_4Cl (aq), and extraction with Et_2O, the organics were washed with water and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (10 : 1 hexane/ethyl acetate) led to 4.3 g (96%) of **90**.

IR (neat) 2990, 1610, 1512, 1364, 1257, 1055, 855, 733 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.97 (s, 3H), 1.33 (s, 3H), 1.43 (s, 3H), 3.13 (A of AB d, J = 10 Hz, 1H), 3.33 (B of AB d, J = 10 Hz, 1H), 3.80 (d, J = 2.0 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (dd, J = 15, 5.3 Hz, 1H), 4.05 (apparent t, J = 5.7 Hz, 1H), 4.36 (dt, J = 5.0, 2.0 Hz, 1H), 4.43 (AB apparent s, 2H), 4.48 (A of AB d, J = 11 Hz, 1H), 4.72 (B of AB d, J = 10 Hz, 1H), 6.76-6.94 (m, 3H), 7.24-7.36 (m, 5H)

HRMS $[M]^+$ calculated : 444.2512, found : 444.2517

Preparation of Alcohol 91 [Scheme 5-1 (cont.)]



To a solution of **90** (4.8 g, 11 mmol) in ethanol stirred at room temperature was added W-2 Raney Ni (~50 g, washed with water then ethanol) and the resultant black slurry was heated at 75°C for 2 h. The mixture was cooled, and filtered through Florisil, washing with additional ethanol and then CH_2Cl_2. The filtrate was concentrated in vacuo, diluted with benzene, dried over $MgSO_4$, filtered and concentrated again. Purification by SiO_2 chromatography (1 : 1 hexane/ether) afforded 3.7 g (98%) of **91**.

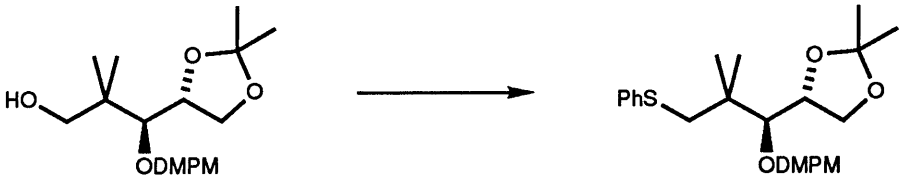
$[\alpha]_D^{24}$ +7.40 (c 0.608, $CHCl_3$)

IR (neat) 3500, 2920, 1515, 1262, 1155, 1040, 855, 800 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.97 (s, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 2.58 (br. s, 1H), 3.38 (AB apparent s, 2H), 3.65 (d, J = 3.1 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.05 (A of ABX m, 1H), 4.08 (B of ABX m, 1H), 4.32 (X of ABX dt, J = 7.1, 3.2 Hz, 1H), 4.60 (A of AB d, J = 11 Hz, 1H), 4.80 (B of AB d, J = 11 Hz, 1H), 6.80-6.97 (m, 3H)

MS (m/z) $[M]^+$ 354, 296, 265, 223, 194, 151

Preparation of Phenyl Sulfide 92 [Scheme 5-1 (cont.)]



91 **92**

To a solution of **91** (3.7 g, 10 mmol) and Et_3N (2.9 mL, 21 mmol) in CH_2Cl_2 (50 mL) stirred at -10°C was added MsCl (1.2mL, 15 mmol) dropwise. The mixture was stirred for 20 min and quenched with water. The aqueous layer was extracted with ether, and the organics were washed with 5% HCl (aq), water, and saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was diluted in DMF (10 mL) and added dropwise to a solution of NaSPh [0.67M in DMF, 60 mL, 40 mmol]. The reaction mixture was heated at ~70°C for 10 h, and was quenched with 10% NaOH (aq). The resulting solution was extracted with ether and the combined organics were washed with water and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (2 : 1 hexane/ether) led to 4.4 g (94%) of **92**.

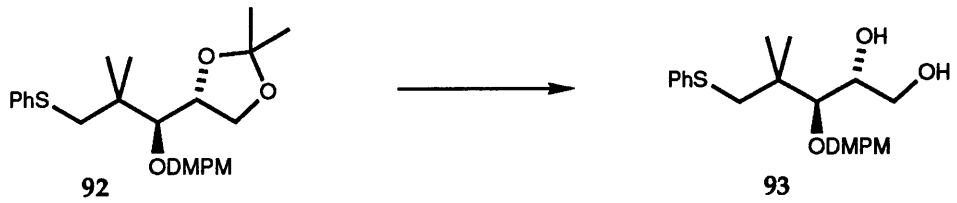
$[\alpha]_D^{24}$ +49.4 (c 0.0769, $CHCl_3$)

IR (neat) 2925, 2225, 1518, 1467, 1364, 1157, 1025, 910, 734 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.06 (s, 3H), 1.36 (s, 3H), 1.47 (s, 3H), 2.88 (A of AB d, J = 12 Hz, 1H), 3.14 (B of AB d, J = 12 Hz, 1H), 3.80 (s, 3H), 3.84 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H), 3.97 (dd, J = 15, 6.9 Hz, 1H), 4.19 (AB apparent t, J = 6.9 Hz, 1H), 4.36 (dt, J = 7.2, 2.3 Hz, 1H), 4.53 (A of AB d, J = 11 Hz, 1H), 4.84 (B of AB d, J = 11 Hz, 1H), 6.73-6.89 (m, 3H), 7.10-7.38 (m, 5H)

MS (m/z) $[M]^+$ 446, 431, 254, 237, 222, 151

Preparation of Diol 93 [Scheme 5-1 (cont.)]



To a solution of **92** (4.4 g, 10 mmol) in methanol (100 mL) was added 6N HCl (aq) (10 mL), and the mixture was stirred for 3 h at room temperature. The reaction was neutralized with solid $NaHCO_3$, concentrated in vacuo, diluted with water, and extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (1: 4 hexane/Et_2O) led to 3.6 g (90%) of **93**.

$[\alpha]_D^{24}$ -22.4 (c 0.125, $CHCl_3$)

IR (neat) 3460, 2930, 2232, 1508, 1457, 1255, 1015, 896, 717 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 1.12 (s, 6H), 2.02 (br. s, 2H), 3.02 (A of AB d, J = 12 Hz, 1H), 3.14 (B of AB d, J = 12 Hz, 1H), 3.65 (d, J = 4.2 Hz, 1H), 3.75-3.94 (m, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 4.59 (A of AB d, J = 11 Hz, 1H), 4.67 (B of AB d, J = 11 Hz, 1H), 6.77-6.90 (m, 3H), 7.11-7.48 (m, 5H)

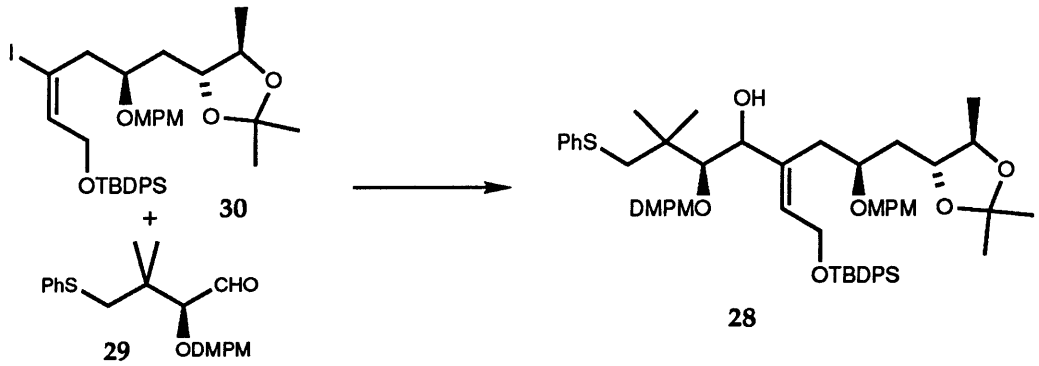
HRMS $[M]^+$ calculated 406.1814, found : 406.1810

Preparation of Fragment C (29) [Scheme 5-1 (cont.)]

To a solution of **93** (1.6 g, 4.0 mmol), water (2 mL), and pH 7 phosphate buffer (aq) (2 mL) in methanol (60 mL) stirred at 0°C was added $NaIO_4$ (0.85 g, 4.0 mmol) portionwise. After 30 min, the reaction mixture was diluted with water, and the resulting solution was extracted with ether. The combined extracts were washed with water and saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Rapid filtration through SiO_2 (2 : 1 hexane/Et_2O) led to 1.3 g (88%) of **29**, which was used immediately in the next step.

^{1}H NMR (300MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.07 (s, 3H), 1.93 (A of AB d, J = 11 Hz, 1H), 3.17 (B of AB d, J = 11 Hz, 1H), 3.67 (d, J = 2.8 Hz, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 4.31 (A of AB d, J = 10 Hz, 1H), 4.50 (B of AB d, J = 10 Hz, 1H), 6.75-6.87 (m, 3H), 7.11-7.38 (m, 5H), 9.74 (d, J = 2.9 Hz, 1H).

Preparation of Alcohol 28 (Scheme 5-3)



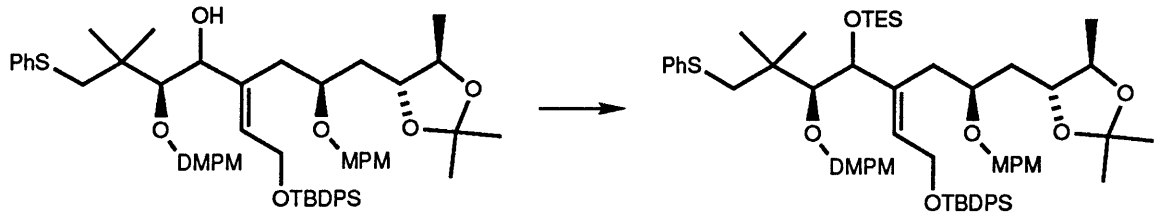
To a solution of **30** (3.6 g, 5.0 mmol) in 10 : 1 ether/THF (70 mL) stirred at -80°C was added *n*-BuLi (2.5M in hexane, 2.0 mL, 5.0 mmol) dropwise over 5 min, and the solution was stirred for an additional 30 min. The reaction mixture was cooled to -100°C, and a solution of **29** (3.0 g, 8.1 mmol) in ether (40 mL), also at -100°C, was added via cannula over 20 min. After an additional 30 min at -100°C, the reaction mixture was transferred via cannula into a flask containing pH 7 phosphate buffer (100 mL). The aqueous layer was extracted with ether, and the combined organics were washed with saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (2 : 1 hexane/ethyl acetate) led to 3.7 g (79%) of **28** as a 6 : 1 mixture of diastereomers (^{1}H NMR).

IR (neat) 3560, 2970, 1633, 1607, 1535, 1485, 1266, 1090, 840, 756, 720 cm^{-1}

^{1}HNMR (300MHz, $CDCl_3$) (When data from the minor diastereomer differs from that of the major, it is reported in [ ].) δ 1.00 (s, 12H), 1.07 (s, 3H), 1.13[1.15] (d, J = 3.6 Hz, 3H), 1.21-1.37 (m, 2H), 1.40-1.53 (m, 2H), 2.14[2.38] (dd, 9.1, 4.8 [9.1, 6.7] Hz, 1H), 2.39[2.53] (dd, J = 9.0, 4.4[9.1, 6.8] Hz, 1H), 2.96 (A of AB d, J = 11 Hz, 1H), 3.14[3.15] (B of AB d, J = 11 Hz, 1H), 3.23 (d, J = 9.5 Hz, 1H), 3.44-3.73 (m, 4H), 3.73 (s, 3H), 3.74 (s, 3H), 3.83[3.79] (s, 3H), 4.20 (t, J = 5.2 Hz, 1H), 4.28-4.46 (m, 4H), 4.42 (A of AB d, J = 6.3 Hz, 1H), 4.63[4.57] (B of AB d, J = 6.7 Hz, 1H), 6.05[5.84] (t, J = 4.0 Hz, 1H), 6.65-6.85 (m, 5H), 7.05-7.47 (m, 13 H), 7.63-7.73 (m, 4H)

HRMS $[M-C_4H_9]^+$ calculated : 905.4119, found : 905.4115

Preparation for Silyl Ether 100 (Scheme 5-4)



28 **100**

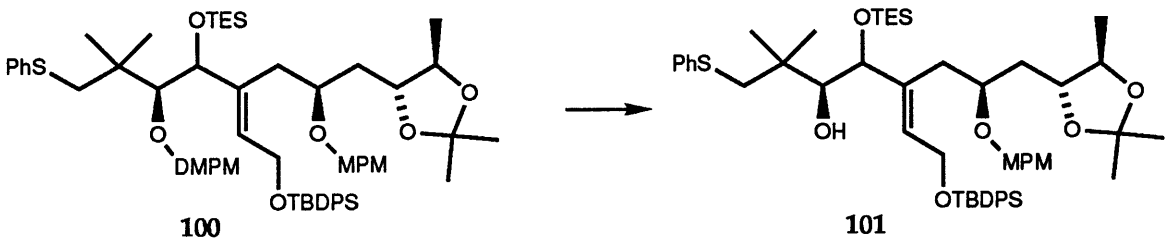
To a solution of **28** (3.7 g, 4.0 mmol) and 2,6-lutidine (1.7 mL, 14 mmol) in CH_2Cl_2 (50 mL) stirred at 0°C was added TES-OTf (1.0 mL, 4.4 mmol) dropwise. After 2 h, ethanol (1 mL) was added and stirring was continued for an additional 1 h. The reaction mixture was then concentrated in vacuo and the resulting cloudy oil was purified by SiO_2 chromatography (4 : 1 hexane/ethyl acetate) to provide 3.9 g (95%) of **100** as a 6 : 1 mixture of diastereomers.

IR (neat) 2950, 1613, 1587, 1514, 1463, 1250, 1070, 816, 730, 695 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) (When data from the minor diastereomer differs from that of the major, it is reported in [ ].) δ 0.67[0.71] (q, J = 6.1 Hz, 6H), 1.01 (t, J = 6.0 Hz, 9H), 1.02 (s, 9H), 1.12 (s, 6H), 1.14 (d, 4.7 Hz, 3H), 1.34 (s, 6H), 1.35-1.67 (m, 2H), 2.25[2.08] (dd, 9.0, 6.1 Hz, 1H), 2.68[2.40] (dd, 9.4, 2.5 Hz, 1H), 2.97[2.95] (A of AB d, 8.3 Hz, 1H), 3.21[3.17] (B of AB d, 8.7 Hz, 1H), 3.47-3.62 (m, 2H), 3.63-3.73 (m, 2H), 3.75 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 4.12-4.58 (m, 6H), 4.68-4.83 (m, 1H), 6.08[6.05] (t, J = 5.4 Hz, 1H), 6.65-6.90 (m, 5H), 7.05-7.45 (m, 13H), 7.57-7.70 (m, 4H)

MS (m/z) $[M]^+$ 1076, 850, 731, 756, 488

Preparation of Alcohol 101 [Scheme 5-4 (cont.)]



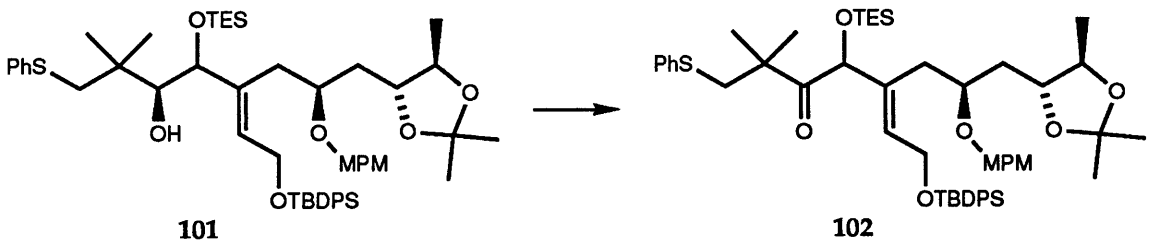
To a mixture of **100** (13.4 g, 14.5 mmol), water (28 mL), and CH_2Cl_2 (520 mL) stirred at 0°C was added a solution of DDQ (3.28 g, 14.5 mmol) in CH_2Cl_2 (100 mL) rapidly. After 30 min the reaction mixture was quenched with saturated Na_2SO_3 (aq), and the organic layer was washed with saturated Na_2SO_3 (aq) and saturated $NaHCO_3$ (aq). The aqueous phases were back-extracted with CH_2Cl_2 and the combined organics were washed with 5% NaOH (aq), water, and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (6 : 1 hexane/ethyl acetate) afforded 7.9 g (68%) of **101** and 1.6 g (12%) of the C(19)-, C(23)-diol, and 1.2 g (8%) of recovered **100**.

IR (neat) 3510, 2950, 1613, 1587, 1513, 1415, 1375, 1243, 11709, 1090, 815, 730, 695 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) (When data from the minor diastereomer differs from that of the major, it is reported in [ ].) δ 0.67 (q, J = 7.8 Hz, 6H), 0.97 (t, J = 7.2 Hz, 9H), 1.05 (s, 15H), 1.14 (d, J = 5.5 Hz, 3H), ~1.1-1.70 (m, 2H), 1.32[1.34] (s, 3H), 2.13 (dd, J = 14, 8.3 Hz, 1H), 2.32 (dd, J = 14, 5.5 Hz, 1H), 3.02 (A of AB d, J = 12 Hz, 1H), ~3.00-3.17 (m, 1H), 3.12 (B of AB d, J = 12 Hz, 1H), 3.34 (d, J = 12 Hz, 1H), 3.46-~3.8 (m, 3H), 3.77[3.75] (s, 3H), 4.16-~4.4 (m, 3H), 4.38 (A of AB d, J = 12 Hz, 1H), 4.46 (B of AB d, J = 10 Hz, 1H), 5.28[5.22] (t, J = 7.2 Hz, 1H), 6.83[6.73] (d, J = 8.3 Hz, 2H), 6.98-7.32 (m, 5H), 7.33-7.52 (m, 8H), 7.60-7.79 (m, 4H)

HRMS $[M-C_4H_9]^+$ calculated : 726.5007, found : 726.5013

Preparation of Ketone 102 [Scheme 5-4 (cont.)]



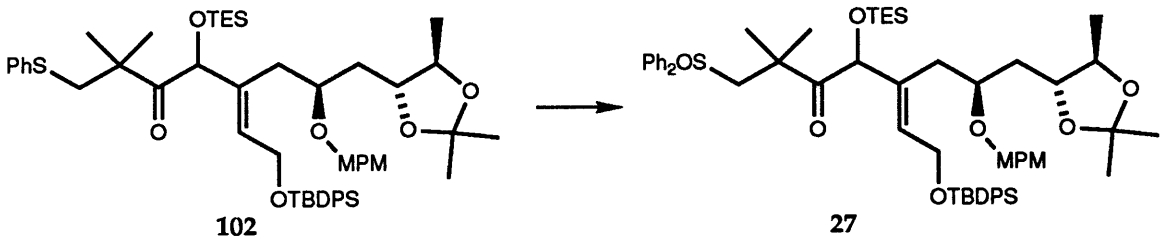
A solution of **101** (7.70 g, 8.32 mmol) in 10 : 1 DMSO/Ac_2O (160 mL) was stirred at room temperature for 10 h. The reaction mixture was diluted with ether and the organics were washed with saturated $NaHCO_3$ (aq), water, and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (7 : 1 hexane/ethyl acetate) led to 6.7 g (87%) of **102** as a 10 : 1 mixture of diastereomers.

IR (neat) 2930, 2240, 1740, 1700, 1610, 1585, 1512, 1465 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) (When data from the minor diastereomer differs from that of the major, it is reported in [ ].) δ 0.63 (q, J = 8.8 Hz, 6H), 0.97 (t, J = 8.6 Hz, 9H), 1.02 (s, 9H), 1.13 (d, J = 5.9 Hz, 3H), ~1.2-1.60 (m, 2H), 1.30 (s, 6H), 1.32 (s, 3H), 1.34 (s, 3H), 2.05 (dd, J = 11, 7.4 Hz, 1H), 2.32 (dd, J = 12, 5.2 Hz, 1H), 3.13 (A of AB d, J = 12 Hz, 1H), 3.34 (B of AB d, J = 12 Hz, 1H), 3.51 (m, 1H), 3.63 (dt, J = 7.8, 1.7 Hz, 1H), 3.76[3.75] (s, 3H), 3.82 (m, 1H), 4.16-~4.4 (m, 2H), 4.38 (A of AB d, J = 10 Hz, 1H), 4.47 (B of AB d, J = 10 Hz, 1H), 4.87[4.93] (s, 1H), 6.06[5.97] (t, J = 5.2 Hz, 1H), 6.79[6.75] (d, J = 7.4 Hz, 2H), 7.08-7.27 (m, 5H), 7.28-7.45 (m, 8H), 7.57-7.70 (m, 4H)

MS (m/z) $[M]^+$ 924, 867, 731, 491

Preparation of Sulfone 27 [Scheme 5-4 (cont.)]



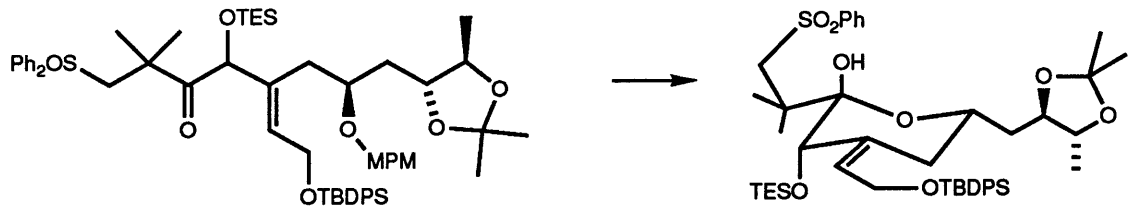
To a solution of **102** (6.60 g, 7.14 mmol) and pyridine (0.40 mL, 5.0 mmol) in CH_2Cl_2 (200 mL) stirred at room temperature was added $MoO_5 \bullet HMPA \bullet H_2O$ (8.0 g, 21 mmol) in one portion. After 48 h an additional quantity of $MoO_5 \bullet HMPA \bullet H_2O$ (4.0 g, 11 mmol) was added and stirring was continued for another 24 h. The reaction mixture was diluted with ether (300 mL), washed with 10% NaOH (aq), water, and saturated NaCl (aq). The ethereal solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (2 : 1 hexane/ethyl acetate) led to 5.94 g (87%) of **27** as a 10 : 1 mixture of diastereomers.

IR (neat) 2925, 2240, 1710, 1613, 1515, 1465, 1448, 1428, 1315, 1306, 1245, 1150, 1100, 905, 818, 725 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) (When data from the minor diastereomer differs from that of the major, it is reported in [ ].) δ 0.67 (q, J = 8.7 Hz, 6H), 0.98 (t, J = 8.4 Hz, 9H), 1.04 (s, 9H), 1.16 (d, J = 5.8 Hz, 3H), ~1.2-1.60 (m, 2H), 1.32[1.34] (s, 6H), 1.43 (s, 3H), 1.62[1.60] (s, 3H), 2.08 (dd, J = 14, 8.1 Hz, 1H), 2.41 (dd, J = 14, 5.6 Hz, 1H), 3.31[3.34] (A of AB d, J = 14 Hz, 1H), 3.53 (m, 1H), 3.66 (dt, J = 7.8, 1.7 Hz, 1H), ~3.7-3.87 {m (B of AB buried), 2H}, 3.77 (s, 3H), 4.32 (m, 2H), 4.44 (A of AB d, J = 11 Hz, 1H), 4.54 (B of AB d, J = 11 Hz, 1H), 5.00[5.07] (s, 1H), 6.07[6.03] (t, J = 6.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.32-7.47 (m, 6H), 7.47-~7.6 (m, 3H), ~7.6-7.73 (m, 4H), 7.85-7.95 (m, 2H)

MS (m/z) $[M]^+$ 956, 899, 841, 824, 820, 819, 713

Preparation of Hemiacetal 103 [Scheme 5-4 (cont.)]



27 103

To a mixture of **27** (5.62 g, 5.88 mmol), water (13.5 mL), and CH_2Cl_2 (270 mL) stirred at 0°C was added DDQ (2.0 g, 8.8 mmol) in one portion. After 20 min, the reaction was quenched with saturated Na_2SO_3 (aq) and the organic phase was washed with saturated Na_2SO_3 (aq) and saturated $NaHCO_3$ (aq). The combined aqueous phases were back-extracted with CH_2Cl_2 and the combined organics were washed with 5% NaOH (aq), water, and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (4 : 1 hexane/ethyl acetate) led to 3.6 g (73%) of **103** which was completely separable from the minor C(20)*R*-diastereomer.

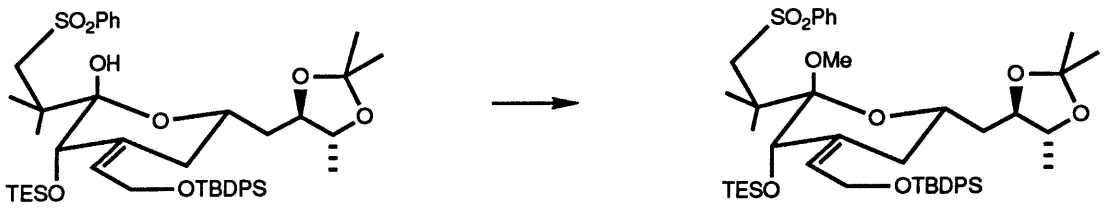
$[\alpha]_D^{24}$ -1.42 (c 0.983, $CHCl_3$)

IR (neat) 3500, 2960, 1650, 1460, 1430, 1380, 1310, 1235, 1145, 1190, 1000, 900, 813, 722 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.55 (q, J = 8.1 Hz, 6H), 0.86 (t, J = 7.8 Hz, 9H), 1.02 (s, 9H), 1.20 (d, J = 6.0 Hz, 3H), ~1.2-1.66 (m, 2H), 1.28 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.94 (AB apparent t, J = 6.6 Hz, 1H), 2.06 (dd, J = 13, 2.5 Hz, 1H), 2.51 (br. s, 1H), 3.37 (A of AB d, J = 15 Hz, 1H), 3.54-~3.7 (m, 2H), ~3.7-~3.8 (m, 1H), 3.77 (B of AB d, 14 Hz, 1H), 3.97 (s, 1H), 4.18 (d, J = 6.3 Hz, 2H), 5.67 (t, J = 6.1 Hz, 1H), 7.32-7.46 (m, 6H), 7.46-~7.6 (m, 3H), ~7.6-7.70 (m, 4H), 7.91 (dd, J = 6.6, 1.7 Hz, 2H)

HRMS $[M-C_4H_9]^+$ calculated : 779.3469, found : 779.3473

Preparation of Methyl Acetal 22 [Scheme 5-4 (cont.)]



103 **22**

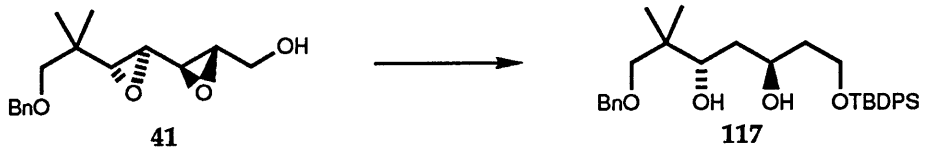
To a solution of $BF_3 \bullet Et_2O$ (0.49 mL, 4.0 mmol) in $(MeO)_3CH$ (50 mL) stirred at 0°C was rapidly added a solution of **103** (3.4 g, 4.0 mmol) in $(MeO)_3CH$ (10 mL). After 4 h, the mixture was quenched with saturated $NaHCO_3$ (aq), and extracted with ether. The organics were washed with 5% HCl (aq), water, and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (5 : 1 hexane/ethyl acetate) led to 2.3 g (69%) of **22**.

IR (neat) 2945, 1450, 1430, 1380, 1315, 1240, 1148, 1176, 845, 820, 730, 697 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 0.53 (q, J = 7.8 Hz, 6H), 0.84 (t, J = 8.1 Hz, 9H), 1.01 (s, 9H), 1.23 (d, J = 6.1 Hz, 3H), ~1.15-1.65 (m, 2H), 1.29 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.95 (AB apparent t, J = 13 Hz, 1H), 2.08 (dd, J = 13, 3.0 Hz, 1H), 3.30 (s, 3H), 3.35-3.50 (m, 1H), 3.60 (m, 1H), 3.70-3.88 (m, 3H), 4.05-~4.1 (m, 1H), 4.15 (d, J = 5.6 Hz, 2H), 5.64 (t, J = 5.6 Hz, 1H), 7.30-7.47 (m, 6H), 7.47-7.61 (m, 3H), 7.61-7.67 (m, 4H), 7.88 (dt, J = 6.5, 1.5 Hz, 2H)

HRMS $[M-C_4H_9]^+$ calculated : 793.3626, found : 793.3622

Preparation of Diol 117 (Scheme 7-2)



41 **117**

To a solution of the bisepoxide **41** (24.6 g, 88.5 mmol) in THF (500 mL) maintained between -60 and -50°C was added Redal (3.4 M in toluene, 130 mL, 442 mmol) dropwise. Over a period of 6 h, the resulting solution was allowed to warm to room temperature and was stirred for 3 d. The reaction mixture was added via cannula to a stirred, saturated solution of Rochelle's salt (aq), and the resulting homogeneous solution was extracted with CH_2Cl_2 and ether. The combined organics were washed with saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. After being azeotroped with toluene, the crude triol was dissolved in CH_2Cl_2 (500 mL). After cooling to 0°C, *i*Pr_2NEt (21.3 mL, 122 mmol), TBDPS-Cl (23.3 mL, 89.7 mmol), and DMAP (0.50 g, 4.1 mmol) were added. The cooling bath was removed and the reaction was allowed to proceed for 20 h before the mixture was diluted with ether. The organics were washed with saturated $NaHCO_3$ (aq) and NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (4:1 hexane/ethyl acetate) led to 36 g (78%, 2 steps) of **117**.

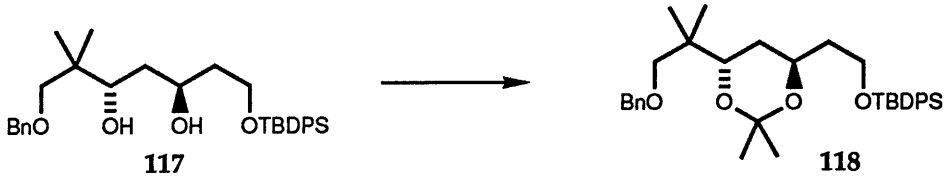
$[\alpha]_D^{24}$ -22.1 (c 0.322, $CHCl_3$)

IR (neat) 3480, 2950, 2880, 1080, 740 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.91 (s, 3H), 1.04 (s, 9H), 1.26 (br. s, 2H), 1.40-1.82 (m, 4H), 3.27 (A of AB d, J = 8.7 Hz, 1H), 3.39 (B of AB d, J = 8.7 Hz, 1H), 3.72 (dd, J = 10, 2.5 Hz, 1H), 3.83 (dt, J = 5.9, 2.9 Hz, 2H), 4.09 (m, 1H), 4.48 (A of AB d, J = 9.1 Hz, 1H), 4.53 (B of AB d, J = 9.2 Hz), 7.25-7.45 (m, 11H), 7.63-7.69 (m, 4H)

MS $[M-H]^+$ 519, 518, 502, 463, 462, 445, 265, 91

Preparation of Acetonide 118 [Scheme 7-2 (cont.)]



117 **118**

To a solution of **117** (35.5 g, 68.3 mmol) and $(MeO)_2CMe_2$ (84 mL, 680 mmol) in CH_2Cl_2 (350 mL) was added catalytic PPTS. After 2 h the reaction mixture was washed with saturated $NaHCO_3$ (aq) and NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (10:1 hexane/ethyl acetate) led to 38 g (99%) of **118**.

$[\alpha]_D^{24}$ -2.27 (c 0.750, $CHCl_3$)

IR (neat) 3510, 2970, 2880, 1460, 1450, 1090, 730 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 0.83 (s, 3H), 0.87 (s, 3H), 1.01 (s, 9H), 1.25 (s, 6H), ~1.30-1.42 (m, 1H), 1.64-1.84 (m, 3H), 3.18 (A of AB d, J = 8.5 Hz, 1H), 3.31 (B of AB d, J = 8.5 Hz, 1H), 3.70 (m, 1H), 3.78 (m, 2H), 3.97 (m, 1H), 4.45 (A of AB d, J = 9.3 Hz, 1H), 4.52 (B of AB d, J = 9.5 Hz, 1H), 7.25-7.46 (m, 11H), 7.62-7.74 (m, 4H)

MS $[M]^+$ 560, 545, 503, 445, 337, 255, 91

Preparation of Alcohol 119 [Scheme 7-2 (cont.)]

118 119

To a deep-blue solution of sodium metal (0.60 g, 26 mmol) in ammonia (200 mL), maintained between -70 and -65°C, was added a solution of **118** (6.8 g, 13 mmol) in ether (20 mL) dropwise. After 30 min, the reaction mixture had faded to pale green and was quenched with NH_4Cl (s) (~3 g) and diluted with ether (150 mL). The ammonia was allowed to evaporate at atmospheric pressure, and the resulting solution was washed with water, saturated $NaHCO_3$ (aq), and NaCl (aq). The aqueous washes were back-extracted with ether and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (5:1 hexane/ethyl acetate) led to 4.8 g (84 %) of alcohol **119**.

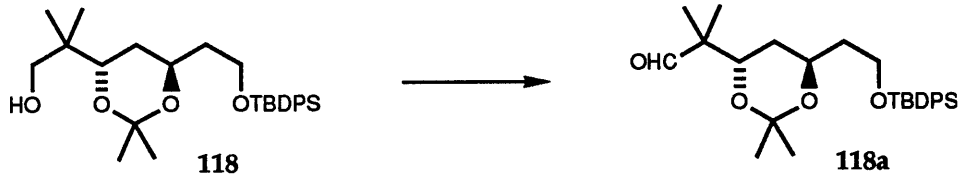
$[\alpha]_D^{24}$ -6.63 (c 1.12, $CHCl_3$)

IR (neat) 3490, 2944, 2880, 1467, 1422, 1090, 734 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.88 (s, 3H), 1.02 (s, 9H) 1.32 (s, 3H), 1.34 (s, 3H), 1.36-1.49 (m, 1H), 1.66-1.92 (m, 3H), 3.01 (t, J = 7.7 Hz, 1H), 3.35 (A of AB dd, J = 8.7, 7.7 Hz, 1H), 3.54 (B of AB dd, J = 8.7, 7.9 Hz, 1H), 3.62-3.82 (m, 3H), 4.01 (m, 1H), 7.32-7.47 (m, 6H), 7.61-7.72 (m, 4H)

HRMS $[M-CH_3]^+$ calculated : 455.2617, found : 455.2618

Preparation of Aldehyde 118a [Scheme 7-2 (cont.)]



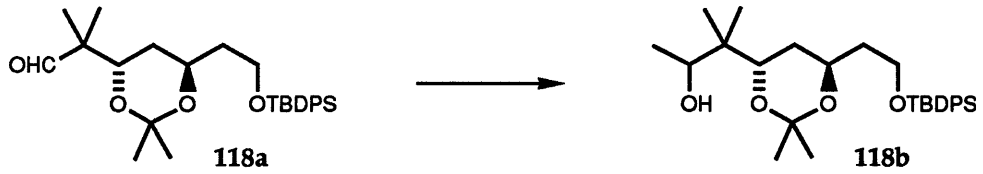
118 **118a**

To a solution of $(COCl)_2$ (2.7 mL, 31 mmol) in CH_2Cl_2 (100 mL) maintained at <-60°C was added DMSO (4.2 mL, 57 mmol) dropwise. After 10 min, a solution of **118** (6.6g, 16 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the reaction mixture was allowed to warm to -45°C over 10 min, and was again cooled to -70°C. Dropwise addition of Et_3N (10 mL, 72 mmol) to the reaction mixture maintained at <-50°C was completed over 5 min and the reaction was brought to -40°C, stirred for 20 min, and quenched with saturated $NaHCO_3$ (aq). The organic layer was washed with water and saturated NaCl (aq), dried over Na_2SO_4, filtered, and concentrated in vacuo. Prior to utilizing crude aldehyde **118a** in the next step, it was azeotroped with toluene. An analytical sample was purified by SiO_2 chromatography (10:1 hexane/ethyl acetate).

IR (neat) 2940, 2880, 2855, 1744, 1460, 1420, 1380, 1210, 1090 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.03 (s, 12H), 1.11-1.46 (m, 2H), 1.32 (s, 3H), 1.43 (s, 3H), 1.68 (apparent q, J = 7.2 Hz, 2H), 3.62-3.74 (m, 1H), 3.75-3.87 (m, 1H), 3.95 (dd, J = 12.0, 1.7 Hz, 1H), 4.13 (m, 1H), 7.32-7.45 (m, 6H), 7.60-7.71 (m, 4H), 9.57 (s, 1H)

Preparation of Alcohol 118b [Scheme 7-2 (cont.)]



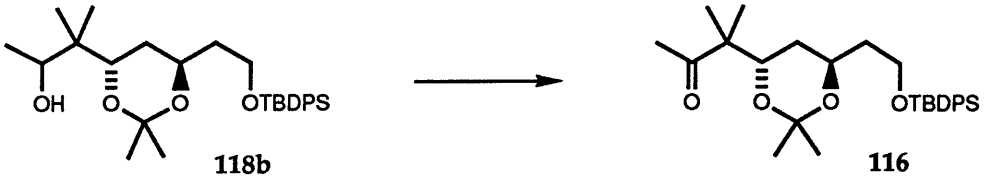
To a solution of crude aldehyde **118a** (6.6 g, ~16 mmol) in THF (100 mL) maintained between -50 and -40 °C was added MeLi (1.7 M in Et_2O, 16 mL, 27 mmol) dropwise. After 5 min, the reaction mixture was quenched with saturated $NaHCO_3$ (aq) and diluted with ether. The organic layer was washed with saturated NaCl (aq), and the aqueous phases were back-extracted with ether. The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. For use in the next reaction crude alcohol **118b** was azeotroped with toluene. An analytical sample was purified by SiO_2 chromatography (5:1 hexane/ethyl acetate).

IR (neat) 3500, 2875, 1440, 1385, 1220, 1175 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 0.67 + 0.84 + 0.86 + 0.87 (s, 6H), 1.02 (s, 9H), 1.06 + 1.08 + 1.11 (s, 3H), 1.15-~1.5 (m, 2H), 1.37 + 1.43 + 1.46 + 1.60 (s, 6H), 1.67 (m, 2H), 3.72 (m, 2H), ~3.75-3.9 (m, 2H), 4.11 (m, 1H), 7.32-7.48 (m, 6H), 7.62-7.72 (m, 4H)

HRMS $[M-H]^+$ calculated : 483.2931, found : 483.2931

Preparation of Fragment A' (116) [Scheme 7-2 (cont.)]



118b **116**

To a solution of $(COCl)_2$ (2.7 mL, 31 mmol) in CH_2Cl_2 (100 mL) maintained at <-60°C was added DMSO (4.2 mL, 57 mmol) dropwise. After 10 min, a solution of crude alcohol **118b** (6.6g, ~16 mmol) in CH_2Cl_2 (5 mL) was added dropwise with maintenance of the reaction temperature at <-70°C. After stirring for 1 h at -70°C, Et_3N (10 mL, 71 mmol) was added dropwise and the reaction mixture was warmed to 0°C over 3 h, and was quenched with saturated $NaHCO_3$ (aq). The organic layer was washed with water and saturated NaCl (aq), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (6:1 hexane/ethyl acetate) led to 5.9 g (87%, 3 steps) of **116**. This ketone was azeotroped with toluene directly before use in the next reaction.

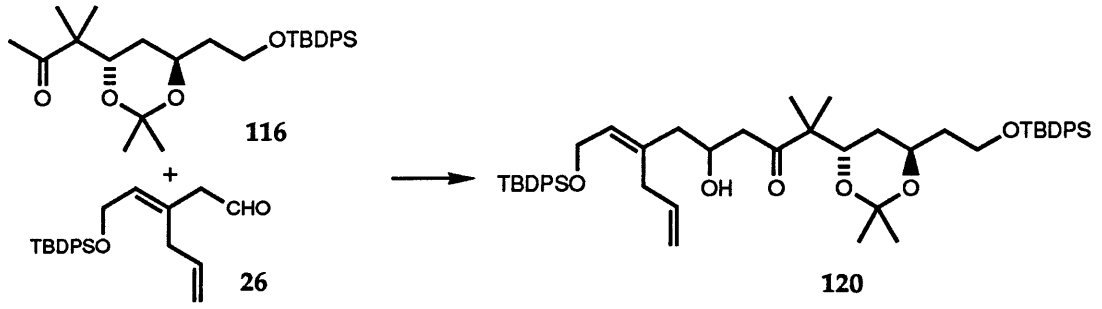
$[\alpha]_D^{24}$ -6.37 (c 1.74, $CHCl_3$)

IR (neat) 2935, 1710, 1433, 1381, 1231, 1172 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 1.02 (s, 12H), 1.10 (s, 3H), 1.27 (s, 3H), 1.28 (s, 3H), 1.38-1.52 (m, 1H), 1.69 (m, 3H), 2.16 (s, 3H), 3.62-3.81 (m, 2H), 3.86-4.02 (m, 2H), 7.28-7.48 (m, 6H), 7.54-7.71 (m, 4H)

HRMS $[M-CH_3]^+$ calculated : 467.2618, found : 467.2621

Preparation of β-Hydroxy Ketone 120 (Scheme 7-3)



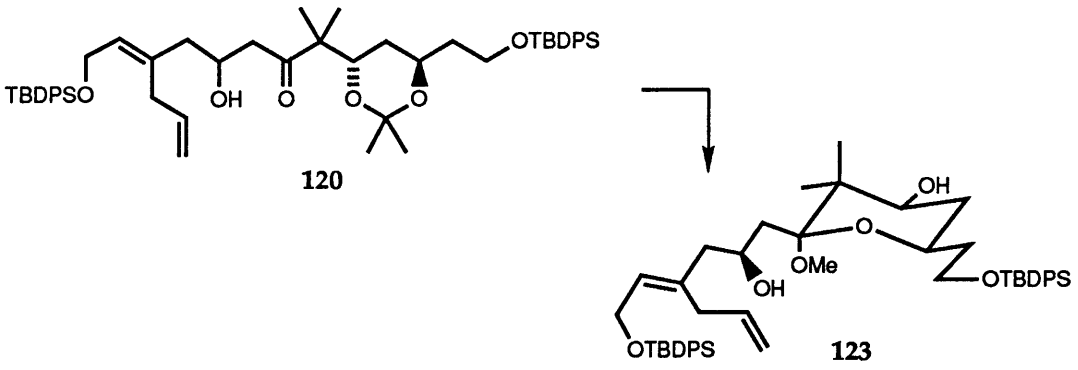
To a solution of **116** (2.3 g, 4.8 mmol) in ether at -70°C was added *i*-Pr_2NEt (3.2mL, 19 mmol) rapidly, and (*R,R*)-1,5-dimethylborolany triflate (**61R**) (1.1 mL, 5.3 mmol) dropwise. After 1 h, a solution of crude **26** (2.4 g, <6.3 mmol) in ether (5 mL) was added dropwise. After an additional hour, the reaction was quenched with N,N-dimethyl ethanolamine (excess) and the mixture was allowed to warm to room temperature. After recovery of the borolanyl amino alcohol complex by filtration, the filtrate was washed with saturated NH_4Cl (aq) and NaCl (aq), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (12:1 --> 6:1 hexane/ethyl acetate) led to 3.5 g (85 %) of coupled **120** as an ~8 : 1 mixture (HPLC) of diastereomers which co-eluted on SiO_2, and 0.30 g (12 %) of recovered **116**.

IR (neat) 2900, 1695, 1460, 1420, 1370, 1095, 1025, 687 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) (When data for the minor isomer differs from that of the major, it is reported in [ ].) δ 1.01 (s, 3H), 1.04 (s, 18H), 1.17 [1.15] (s, 3H), 1.30 (s, 6H), 1.43-1.58 (m, 1H), 1.67-1.83 (m, 3H), 2.06-2.32 (m, 2H), 2.55-2.87 (m, 4H), 3.06 [3.03] (d, 2.3 Hz, 1H), 3.77 (m, 2H), 4.00 (m, 2H), 4.17 (br. s, 1H), 4.25 (A of AB d, J ~ 9 Hz, 1H), 4.33 (B of AB d, J = 9.2 Hz, 1H), 4.90-5.05 (m, 2H), 5.53-5.75 (m, 2H), 7.32-7.53 (m, 12H), 7.65-7.82 (m, 8H)

HRMS $[M-C_4H_9]^+$ calculated : 803.4163, found : 803.4158

Preparation of Methyl Acetal 123 (Scheme 7-4)



To a solution of **120** (9.5 g, 11 mmol) in methanol (200 mL) and $HC(OMe)_3$ (50 mL) stirred at 24°C was added PPTS (~200 mg). After 7 h at room temperature the reaction mixture was diluted with ether and washed with pH 7 phosphate buffer. The aqueous phase was separated and back-extracted with ether. The combined organics were washed with saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (8 : 1 hexane/ethyl acetate) allowed for complete separation of the C(11)-diastereomers yielding 6.2g (65%) of **123** and 0.79 g (8.3 %) of the C(11)*R*-diastereomer.

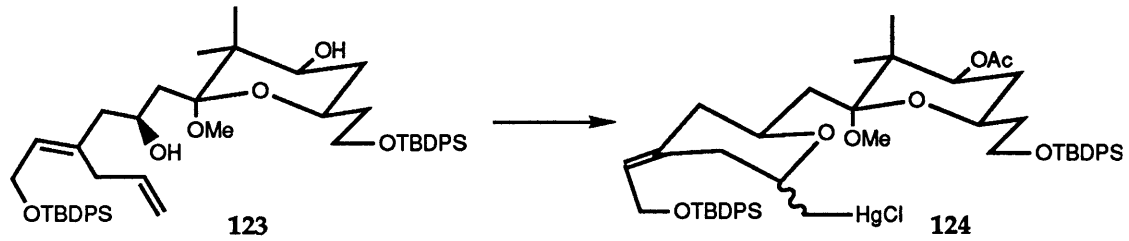
$[\alpha]_D^{24}$ -6.47 (c 0.988, $CHCl_3$)

IR (neat) 3410, 2925, 2210, 1694, 1138, 1010, 900 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.01 (s, 3H), 1.04 (s, 18H), 1.33-1.45 (m, 1H), 1.58-1.83 (m, 3H), 1.84-1.98 (m, 2H), 2.05 (dd, J = 13, 6.6 Hz, 1H), 2.25 (dd, J = 13, 6.4 Hz, 1H), 2.67 (m, 2H), 3.19 (s, 3H), 3.43 (s, 1H), 3.72 (m, 1H), 3.86 (m, 1H), 3.90-4.06 (m, 2H), 4.16 (m, 1H), 4.24 (d, J = 6.3 Hz, 2H), 4.89 (m, 1H), 4.95 (m, 1H), 5.54-5.69 (m, 2H), 7.33-7.45 (m, 12H), 7.61-7.73 (m, 8H)

MS $[M]^+$ 834, 833, 816, 802, 771, 616

Preparation of Organomercurial Chloride 124 [Scheme 7-4 (cont.)]



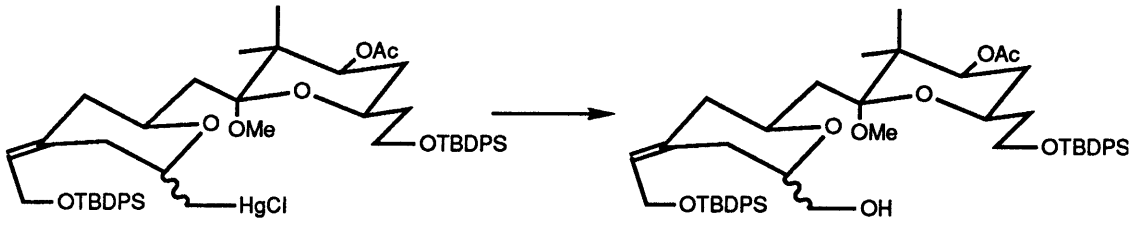
To a solution of **123** (6.2 g, 7.2 mmol) in THF (170 mL) and methanol (70 mL) stirred at room temperature was added $Hg(OAc)_2$ (3.3 g, 10.0 mmol), in 550 mg portions, every hour for 6 h. The reaction mixture was then quenched with saturated KCl (aq) (40 mL), stirred for an additional 10 min, and diluted with ether. The organics were washed with saturated $NaHCO_3$ (aq) and concentrated in vacuo. After being azeotroped twice with benzene, the crude material was dissolved in pyridine (40 mL), and DMAP (~30 mg) and Ac_2O (5.6 mL, 57 mmol) were added. After 10 h at room temperature, the reaction mixture was diluted with ether, and washed with saturated $CuSO_4$ (aq), water, and saturated NaCl (aq). The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (4 : 1 hexane/ethyl acetate) afforded 7.3 g (93 %) of **124**.

IR (neat) 3450, 2940, 2228, 1700, 1459, 1424, 1060, 900, 725, 694 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 0.91 + 0.92 + 1.02 + 1.03 (s, 6H), 1.04 + 1.06 (s, 18H), 1.30-2.35 (m, 10H), 2.04 (s, 3H), 3.09 + 3.12 (s, 3H), 3.18 (m, 1H), 3.51 (m, 1H), 3.72 (m, 1H), 3.83 (m, 3H), 4.13 (m, 1H), 4.20 (d, J = 6.7 Hz, 2H), 5.18 + 5.23 (t, J = 5.2 Hz, 1H), 5.37 + 5.44 (t, J = 7.0 Hz, 1H), 7.32-7.47 (m, 12H), 7.58-7.73 (m, 8H)

MS $[M\text{-}CH_3]^+$ 1097, 1055, 1053, 1021, 963, 843, 787, 785

Preparation of Alcohol 125 [Scheme 7-4 (cont.)]



124 **125**

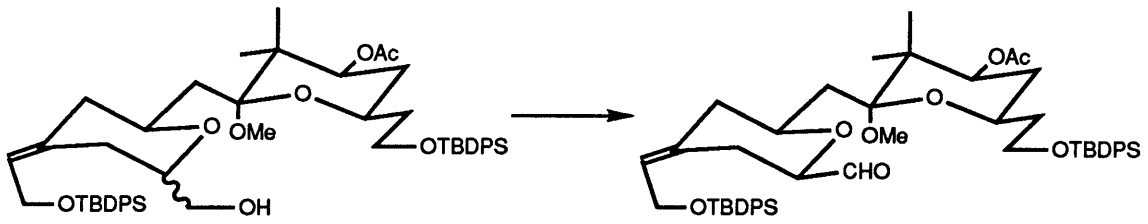
Through a solution of **124** (3.6 g, 3.3 mmol) in CH_2Cl_2 (50 mL) was passed a steady stream of O_2 for 10 min from a compressed gas cylinder via a glass capillary tube (solution volume was maintained at by replacing evaporated CH_2Cl_2 via syringe). In a separate vessel, a slurry of $NaBH_4$ (500 mg, 13 mmol) was stirred in DMF (100 mL) and flushed with oxygen in a similar manner for 2-3 min. The CH_2Cl_2 solution was then slowly added to the DMF solution via cannula over a period of 1 h. After stirring for an additional 1 h, with a continual flow of O_2, the reaction was quenched with saturated NH_4Cl (aq), and extracted with ether. The combined organic extract was washed with water and saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (5:1 hexane/ethyl acetate) led to 2.2 g (77%) of **125** as a 1 : 1 mixture of partially separable diastereomers.

IR (neat) 3420, 2925, 1740, 1697, 1150, 1010 cm-1

^{1}H NMR (300MHz, $CDCl_3$) δ 0.92 + 0.94 + 1.00 + 1.02 (s, 6H), 1.04 (s, 18H), 1.18-2.28 (m, 10H), 2.07 (s, 3H), 3.09 + 3.13 (s, 3H), 3.16-3.57 (m, 3H), 3.69 (m, 2H), 3.76-4.04 (m, 3H), 4.22 + 4.24 (d, J = 6.9 Hz, 2H), 5.23 (m, 1H), 5.42 + 5.47 (t, J = 7.3 Hz, 1H), 7.32-7.47 (m, 12 H), 7.58-7.74 (m, 8H)

HRMS $[M\text{-}CH_3O]^+$ calculated : 861.4582, found : 861.4576

Preparation of Aldehyde 115 [Scheme 7-4 (cont.)]

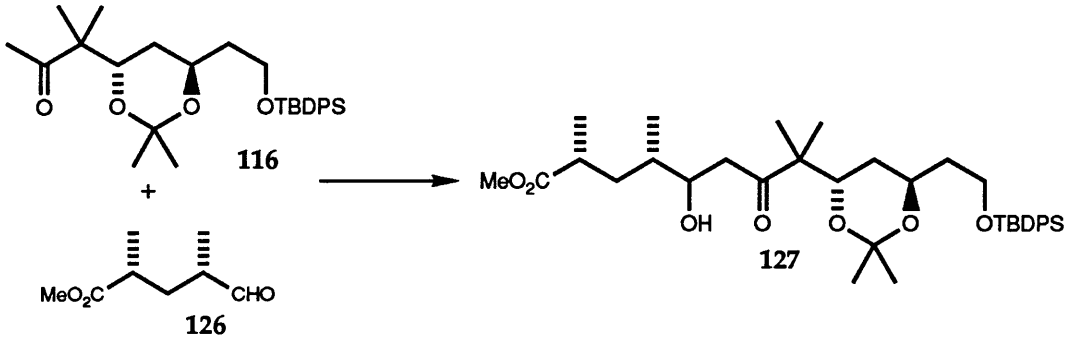


125 **115**

To a solution of $(COCl)_2$ (0.18 mL, 2.0 mmol) in CH_2Cl_2 (10 mL) stirred at -78°C was added DMSO (0.32 mL, 4.4 mmol) dropwise. After 10 min, a -78°C solution of **125** (0.58 g, 0.68 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After stirring for 2 h at -78°C, Et_3N (0.86 mL, 6.1 mmol) was added dropwise, and stirring was continued for an additional 2 h. The reaction mixture was quenched with a pH 7 phosphate buffer solution at -78°C and and the aqueous layer was extracted with CH_2Cl_2. The combined organics were diluted with ether and washed with 5% HCl (aq) and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash filtration on SiO_2 (5 : 1 hexane/ethyl acetate) led to 0.56 g (96 %) of **115** as a 1 : 1 mixture of inseparable diastereomers which was dissolved in benzene (40 mL) and stirred with DBU (0.22 mL, 1.3 mmol) for 8 h. The reaction mixture was diluted with ether, and washed with 5% HCl (aq), water, and saturated NaCl (aq). The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. This two step process led to 0.53 g (92 % overall) of **115** as a 5 : 1 diastereomeric mixture. The diastereomeric purity was easily increased by reducing to the alcohol [$NaBH_4$ (60 mg, 1.6 mmol) in *i*PrOH (15 mL)], almost complete separation of the cis/trans diastereomers, and oxidation of the predominantly cis isomer. In this way, the trans isomer was also converted to the cis, and a total of 0.46 g of **115** (80% yield from diastereomerically 1 : 1 **125**) was obtained.

^{1}H NMR (300MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.14 (s, 3H), 1.17 (s, 18H), ~1.30-1.92 (m, 4H), 1.73 (s, 3H), 2.10-2.25 (m, 2H), 2.37-2.49 (m, 1H), 3.03 (s, 3H), 3.22 (dd, J = 9.3, 2.0 Hz, 1H), 3.56 (m, 1H), 3.72-3.93 (m, 4H), 4.27 (d, J = 6.8 Hz, 2H), 5.50-5.63 (m, 2H), ~7.20-7.40 (m, 12H), 7.72-7.91 (m, 8H), 9.47 (s, 1H).

Preparation of β-Hydroxy Ketone 127 (Scheme 7-5)



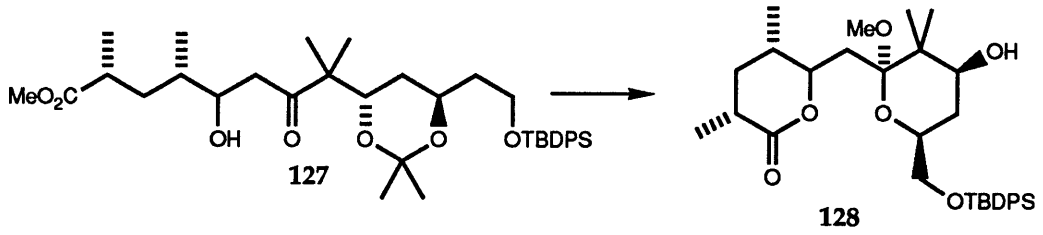
To a magnetically stirred solution of ketone **116** (412 mg, 0.854 mmol) in ether (10 mL) at -78°C was added *i*-Pr_2EtN (0.59 mL, 3.42 mmol) followed by the dropwise addition of triflate **61R** (0.19 mL, 0.94 mmol). The reaction mixture was stirred at -78°C for 30 min and subsequently warmed to -25°C and stirred for 10 min. The reaction mixture was cooled to -78°C, and a solution of aldehyde **126** (155 mg, 0.982 mmol) in ether (1 mL) was added dropwise via cannula and the resultant mixture was stirred at -78°C for an additional 2 h. The reaction was quenched by addition of 2-amino-2-methyl-1-propanol (0.24 mL, 2.56 mmol), warmed to -20°C over 1.5 h, and diluted with saturated NH_4Cl (aq) and ether. The organic layer was separated and washed with water and saturated NaCl (aq), and dried over $MgSO_4$. After filtration and concentration in vacuo, SiO_2 chromatography (4:1 hexane/ethyl acetate) led to 514mg (94%) of **127** as a 25 : 1 mixture of diastereomers (HPLC).

IR (neat) 3440, 3080, 2950, 1740, 1700, 1100 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) δ 0.87 (d, J = 6 Hz, 3H), 1.02 (s, 9H), 1.09 - 1.34 (m, 14H), 1.36 - 1.88 (m, 8H), 2.46 - 2.73 (m, 3H), 3.65 (s, 3H), 3.70 (m, 1H), 3.92 (m, 3H), 7.39 (m, 6H), 7.63 (m, 4H)

MS m/z $[M]^+$640, 623, 585, 565

Preparation of Lactone 128 [Scheme 7-5 (cont.)]

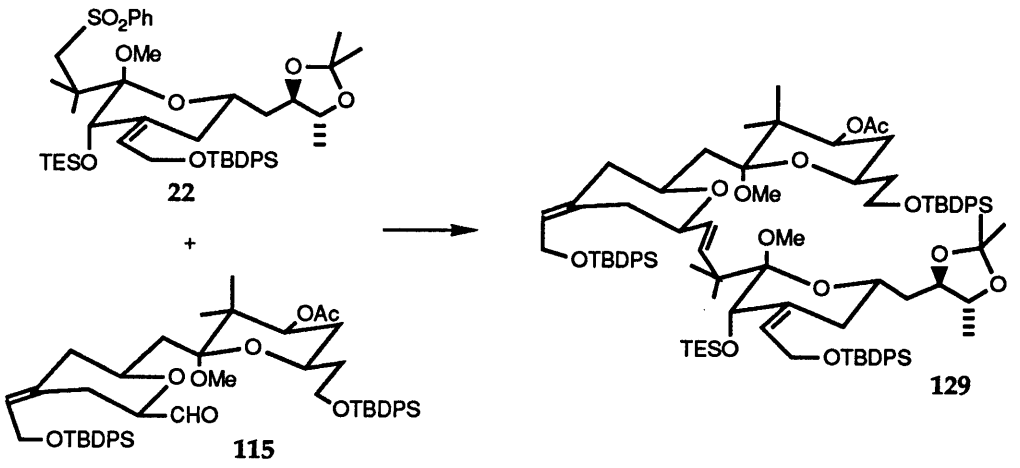


To a magnetically stirred solution of **127** (25:1 diastereomeric mixture) (486 mg, 0.79 mmol) in 3 : 1 MeOH/$(MeO)_3CH$ (12 mL) at ambient temperature was added one crystal of PPTS. After stirring for 6 h, the reaction mixture was poured into a solution of ether and pH 7 phosphate buffer. The organic layer was separated, washed with water and saturated NaCl (aq), and dried over $MgSO_4$. Filtration and and concentration in vacuo afforded the crude acetal which was dissolved in a 1 : 1 THF/water (15 mL), cooled to 0°C and treated with LiOH (aq) (1.5 mL, 1M solution, 1.5 mmol). After stirring at ambient temperature for 12 h, the reaction mixture was acidified to pH 4 by addition of 1M HCl (aq). The organic phase was separated and the aqueous phase was back-extracted with ethyl acetate. The combined organic extract was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the carboxylic acid (477 mg crude) which was dissolved in CH_2Cl_2 (10 mL). At ambient temperature, one crystal of DMAP was added followed by DCC (253 mg, 1.22 mmol). After stirring for 2 h, the precipitates were filtered and the filtrate was washed with water, 5% acetic acid (aq), and again water. The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (3 : 1 hexane/ethyl acetate) led to 359 mg (79%, 3 steps) of lactone **128**.

^{1}H NMR (300MHz, $CDCl_3$) δ 0.77 - 1.08 (m, 15H), 1.10 - 1.43 (m, 15H), 2.45 (m, 1H), 3.11 (s, 3H), 3.61 - 3.90 (m, 3H), 3.95 (dd, J = 11, 5 Hz, 1H), 4.22 (ddd, J = 10, 6, 6 Hz, 1H), 7.39 (m, 6H), 7.63 (m, 4H)

MS m/z $[M\text{-}OMe]^+$ 551 ,511

Preparation of *E*-Olefin 129 (Scheme 8-1)



To a solution of sulfone **22** (0.94 g, 0.96 mmol) in THF (9.6 mL) stirred at -78°C was added PhLi (0.96 M in Et_2O, 1.2 mL, 1.2 mmol) dropwise, which caused immediate yellowing (i.e. formation of the lithiated sulfone). After stirring for 30 min, aldehyde **115** (0.71 g, 0.80 mmol) in THF (6 mL) was added dropwise. After stirring for an additional hour at -78°C, PhCOCl (0.27 mL, 2.3 mmol) and DMAP (30 mg, 0.25 mmol) were added, the cooling was bath removed, and the reaction was allowed to proceed at ambient temperature. After 10 h, the reaction was quenched with $Me_2NCH_2CH_2NH_2$ (0.60 mL, 4.8 mmol), stirred for 1 h, diluted with saturated NH_4Cl (aq), and extracted with ethyl acetate. The combined organic phases were washed with saturated NH_4Cl (aq), saturated $NaHCO_3$ (aq), and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (20 : 1 --> 10 : 1 benzene/ethyl acetate) afforded 1.3 g of the benzoate which was dissolved in 2 : 1 methanol/ethyl acetate (45 mL) and cooled to -20 °C. After the rapid addition of 5% Na-Hg (6 g) and Na_2HPO_4 (3g) the reaction mixture was stirred at -20°C. After 2 h, an additional portion of 5% Na-Hg (3 g) was added. After a final 3 h, the mixture was diluted with ethyl acetate, and the organic phase decanted and washed with saturated NH_4Cl (aq). The aqueous washes were back-

extracted, and the combined organics were washed with saturated $NaHCO_3$ (aq) saturated NaCl (aq). Purification was accomplished with SiO_2 chromatography (20 : 1 --> 10 : 1 --> 2 : 1 hexane/ethyl acetate) to afford 0.77g (60% based on aldehyde, 2 steps) of *E*-olefin **129**.

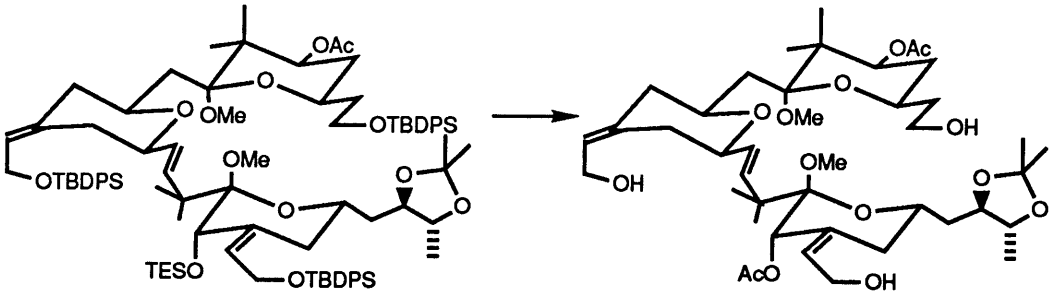
$[\alpha]_D^{24}$ +27.0 (c 0.074, $CHCl_3$)

IR (neat)3076, 2956, 1743, 1476, 1431, 1377, 1242 cm^{-1}

^{1}H NMR (250 MHz, C_6D_6) δ 0.72 (q, J = 7.9 Hz, 6H), 1.03 (t, J = 7.9 Hz, 9H), 1.07-2.47 (m, 14H), 1.17 (br. s, 27H), 1.42 (s, 6H), 1.45 (s, 3H), 1.47 (s, 3H), 1.69 (s, 3H), 3.12 (s, 3H), 3.41 (s, 3H), 3.56 (m, 1H), 3.64-4.02 (m, 11H), 4.29 (d, J = 6.1 Hz, 2H), 4.30 (s, 1H), 4.38 (d, J = 6.0 Hz, 2H), 5.50-5.62 (m, 3H), 5.84 (t, J = 6.1 Hz, 1H), 6.39 (d, J = 16.2 Hz, 1H), 7.15 (m, 18H), 7.80 (m, 12H)

MS (m/z) $[M]^+$ 1583

Preparation of Acetate 130 [Scheme 8-1 (cont.)]



129 **130**

To a solution of tetrasilyl ether **129** (0.77 g, 0.48 mmol) in THF (5 mL) stirred at ambient temperature was added *n*-Bu_4NF (1 M solution in THF, 9.6 mL, 9.6 mmol). After 2 h, the reaction mixture was diluted with saturated NH_4Cl (aq) and extracted with ether. The combined organics were washed with with water, saturated $NaHCO_3$ (aq), and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude tetraol. This oil was immediately dissolved in DMF (15 mL), treated with imidazole (0.65 g, 9.6 mmol) and TBDM-Cl (0.72 g, 4.8 mmol), and stirred at room temperature. After 12 h, the reaction mixture was diluted with saturated NH_4Cl (aq) and extracted with ethyl acetate. The combined organics were washed with saturated $NaHCO_3$ (aq), saturated NaCl (aq), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the crude trissilyl ether. This oil was dissolved in pyridine (4.4 mL) at ambient temperature and Ac_2O (1.1 mL) was added, followed by DMAP (10 mg). After 3 h, the reaction mixture was quenched with water, stirred for 1 h at room temperature, and extracted with ethyl acetate. The combined organics were washed with saturated $CuSO_4$ (aq), water, saturated $NaHCO_3$ (aq), and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude acetate. To the resulting oil, dissolved in THF (5 mL) stirred at ambient temperature, was added *n*-Bu_4NF (1 M in THF, 10 mL, 10 mmol) in one portion. After stirring for 2 h, the mixture was diluted with saturated NH_4Cl (aq), and

extracted with ether. The combined organic phases were washed with ether, saturated $NaHCO_3$ (aq), and saturated NaCl (aq), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by SiO_2 chromatography (2 : 1 hexane/ethyl acetate --> 10 : 1 CH_2Cl_2/methanol) afforded 0.38 g (100%, 4 steps) of triol **130** as a viscous oil.

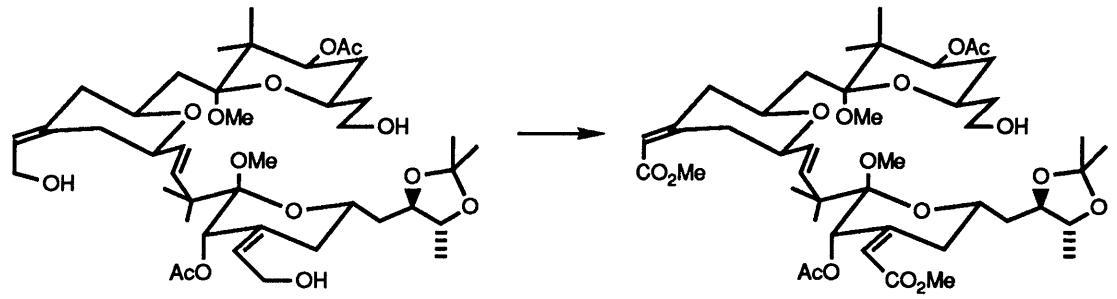
$[\alpha]_D^{24}$ +38.8 (c 0.067, $CHCl_3$)

IR (neat) 3442, 2980, 1731, 1437, 1374, 1245

^{1}H NMR (250 MHz, C_6D_6) δ 1.10 (s, 3H), 1.17 (s, 3H), 1.21 (d, J = 6.0 Hz, 3H), 1.38 (s, 6H), 1.41 (s, 6H), 1.51-2.28 (m, 16H), 1.70 (s, 3H), 1.81 (s, 3H), 2.65 (d, J = 12.5 Hz, 1H), 3.06 (s, 3H), 3.43 (s, 3H), 3.61 (m, 5H), 3.92-4.07 (m, 7H), 5.52 (dd, J = 11.6, 4.9 Hz, 1H), 5.51 (t, J = 6.0 Hz, 1H), 5.64 (dd, J = 16.9, 5.1, 1H), 5.72 (s, 1H), 5.88 (t, J = 6.1 Hz, 1H), 6.34 (d, J = 16.9 Hz, 1H)

HRMS $[M-C_2H_8O_2]^+$ calculated : 732.4085, found 732.4092

Preparation of alcohol 131 [Scheme 8-1 (cont.)]



130 **131**

To a solution of triol **130** (0.28 g, 0.35 mmol) in THF (14 mL) was added MnO_2 (1.5 g) After 30 min, more MnO_2 (1.5 g) was added to complete the oxidation and stirring was continued for an additional 30 min. The reaction mixture was then diluted with anhydrous methanol (42 mL), cooled to 0°C, and treated with MnO_2 (2.9 g), followed by the addition of NaCN (80 mg), and AcOH (80μl). The cooling bath was removed and the reaction was allowed to proceed for 12 h at ambient temperature. The mixture was subsequently filtered through Celite, and the precipitates were washed with ethyl acetate. The filtrate was diluted with saturated NH_4Cl (aq), and extracted with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$ (aq) and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (1 : 1 --> 1 : 2 hexane/ethyl acetate) afforded 0.18 g (61%) of bismethyl ester **131**.

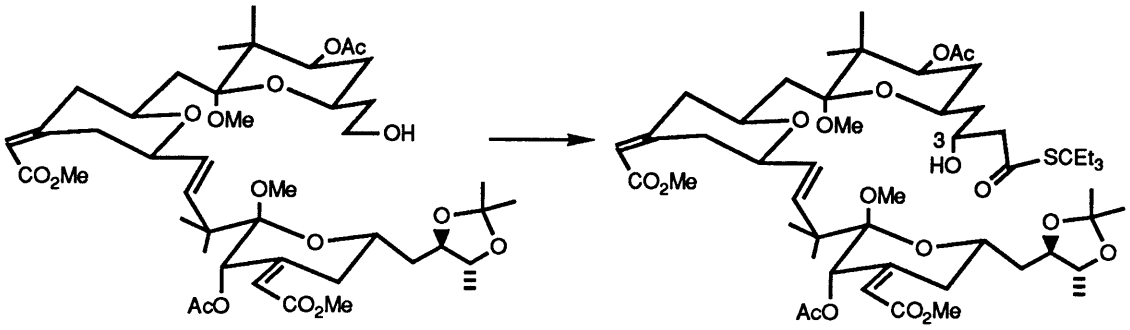
$[\alpha]_D^{24}$ +38.3 (c 0.094, $CHCl_3$)

IR (neat) 3532, 2986, 2950, 1725, 1656, 1440, 1374, 1245

^{1}HNMR (250 MHz, C_6D_6) δ 1.08 (s, 3H), 1.13 (s, 3H), 1.19 (d, J = 5.9 Hz, 3H), 1.27 (br. s, 6H), 1.30-2.20 (m, 14 H), 1.38 (s, 6H), 1.71 (s, 3H), 1.80 (s, 3H), 2.51 (m, 1H), 3.01 (s, 3H), 3.34 (s, 3H), 3.37 (s, 3H), 3.40 (s, 3H), 3.45-4.33 (m, 8H), 5.50 (dd, J = 11.6, 4.6 Hz, 1H), 5.55 (dd, J = 14.9, 4.9 Hz, 1H), 5.82 (s, 1H), 6.22 (s, 1H), 6.36 (d, J = 14.9 Hz, 1H)

MS (m/z) $[M]^+$ 851

Preparation of β-Hydroxythioester 135 [Schemes 8-1 (cont.) and 8-2]



131 135

To a solution of $(COCl)_2$ (0.087 ml, 1.0 mmol) in CH_2Cl_2 (10 mL) stirred at -78°C was added DMSO (0.14 mL, 2.0 mmol) dropwise. After 5 min, a solution of alcohol **131** (0.17 g, 0.20 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78°C, quenched with Et_3N (0.36 mL, 2.6 mmol), warmed to 0°C, and stirred for 30 min. The reaction was quenched with saturated NH_4Cl (aq) and extracted with ethyl acetate. The combined organic phases were washed with saturated NH_4Cl (aq), saturated $NaHCO_3$ (aq), and saturated NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 chromatography (hexane --> 2 : 1 hexane/ethyl acetate) afforded 0.17g (100%) of aldehyde **114** which was immediately used in the next step. To a solution of aldehyde **114** in Et_2O (10 mL), stirred at -100°C was added the chiral boron enolate **57S** (0.1M in Et_2O, 5 mL, 0.5 mmol) [prepared by adding (*S,S*)-2,5-dimethy-borolanyl triflate (0.41 mL, 2 mmol) dropwise to a solution of $Et_3CSC(O)Me$ (0.35 g, 2.0 mmol) and *i*-Pr_2NEt (0.52 mL, 3.0 mmol) in Et_2O (20 mL) and stirring for 30 min at -78 °C]. The reaction mixture was warmed to -78°C and stirred for 30 min, quenched with 2-amino-2-methyl-1-propanol (3.7 g, 50 mmol), and stirred for 2 h at ambient temperature. The resulting solution was diluted with saturated NH_4Cl (aq), and extracted with ethyl acetate. The combined organic phases were washed with saturated NH_4Cl (aq), saturated $NaHCO_3$

(aq), and saturated NaCl (aq), and concentrated in vacuo. Purification by SiO_2 chromatography (hexane --> 2 : 1 hexane/ethyl acetate) afforded 0.17 g (83%) of **135** as a 3 : 1 mixture of C(3)-diastereomers.

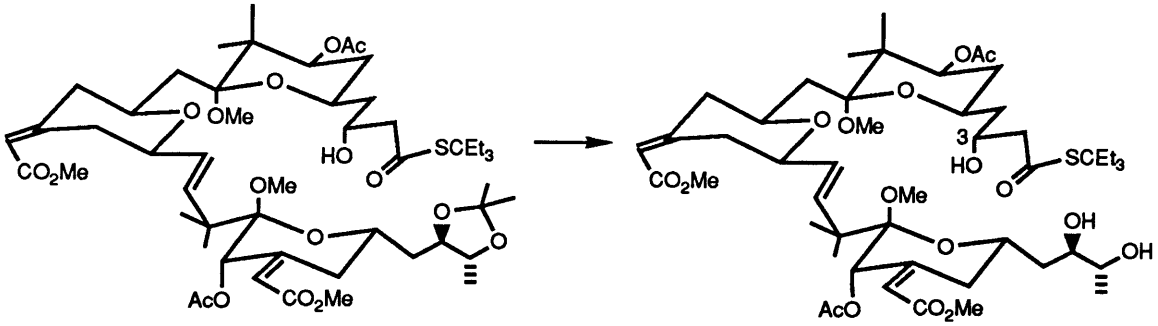
$[\alpha]_D^{24}$ +28.3 (c 0.092, $CHCl_3$)

IR (neat) 3520, 2980, 1722, 1674, 1461, 1440, 1374, 1236 cm^{-1}

^1H NMR (250 MHz, $CDCl_3$) (When data from the minor diastereomer differs from that of the major, it is reported in [ ].) δ 0.87 (t, J = 7.5 Hz, 9H), 0.91 (s, 3H), 1.01 (s, 3H), 1.11 (d, J = 5.1 Hz, 3H), 1.18-1.31 (m, 11H), 1.33 (s, 3H), 1.30 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.78 (q, J = 7.4 Hz, 6H), 2.04 (s, 3H), 2.08 (s, 3H), 2.31 (m, 3H), 2.65 (m, 3H), 3.21 (s, 3H), 3.22 [3.05] (d, J = 4.4 [3.8] Hz, 0.75 [0.25] H), 3.34 (s, 3H), 3.69 (s, 6H), 3.47-4.28 (m, 6H), 5.18 (dd, J = 11, 4.7 Hz, 1H), 5.38 (dd, J = 16, 4.7 Hz, 1H), 5.43 (s, 1H), 5.69 (s, 1H), 5.89 (s, 1H), 6.10 (d, J = 16 Hz, 1H)

HRMS $[M-2xCH_3OH]^+$ calculated : 960.4905, found 960.4903

Preparation of Triol 113 (Scheme 8-3)



135 **113**

To a solution of acetonide **135** (63 mg, 0.060 mmol) in anhydrous methanol (6 mL) was added CSA (14 mg) and stirring was continued at ambient temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (aq), and extracted with ethyl acetate. The combined organic phases were washed with saturated NaCl (aq), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparative TLC (1 : 1 benzene/ethyl acetate, 3 developments) afforded 18 mg (30%) of triol **113**, 25 mg (40%) of recovered **135** (which was recycled), and 10 mg (~17%) of a lower R_f product.

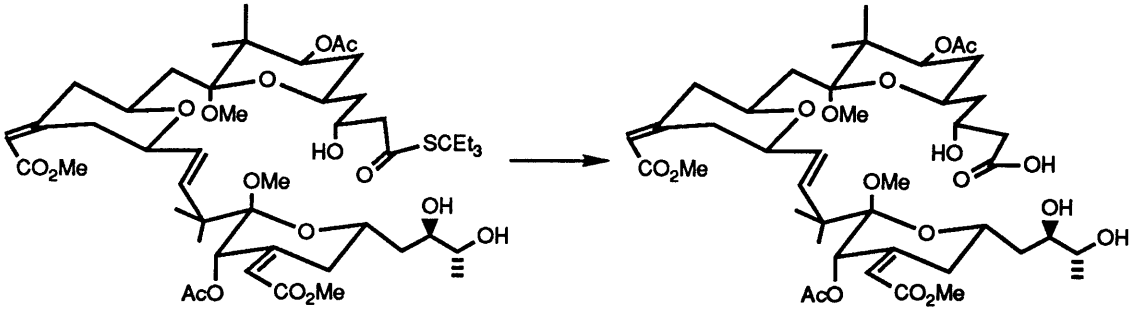
$[\alpha]_D^{24}$ +32.1 (c 0.162, $CHCl_3$)

IR (neat) 3532, 3024, 2976, 1722, 1660, 1462, 1440, 1374, 1240, 1218 cm^{-1}

^{1}H NMR (250 MHz, C_6D_6) δ 0.82 (t, J = 7.3 Hz, 9H), 1.09 (s, 3H), 1.13 (d, J = 5.9 Hz, 3H), 1.14 (s, 3H), 1.25 (s, 6H), 1.30-2.15 (m, 16H), 1.71 (s, 6H), 1.78 (q, J = 7.3 Hz, 6H), 2.53 (m, 2H), 3.10 (s, 3H), 3.34 (s, 6H), 3.42 (s, 3H), 3.48 (m, 1H), 3.74-3.92 (m, 4H), 4.17-4.38 (m, 3H), 5.56 (dd, J = 15.9, 4.8 Hz, 1H), 5.59 (m, 1H), 5.78 (s, 1H), 5.86 (s, 1H), 6.24 (s, 1H), 6.37 (d, J = 15.9 Hz, 1H)

HRMS calculated : 920.4592, found : 920.4596

Preparation of Seco Acid Derivative 138 (Scheme 8-4)



113 **138**

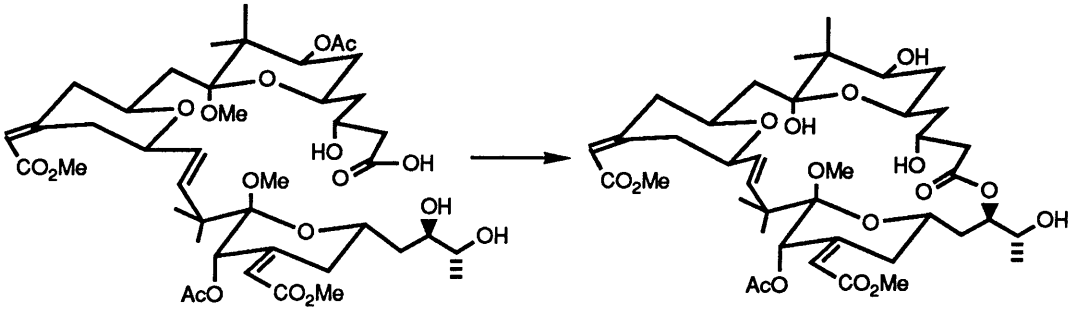
To a solution of triol **113** (27 mg, 0.027 mmol) in CH_2Cl_2 (3 mL) stirred at 0°C was added lutidine (0.18 mL, 1.2 mmol) and TES-OTf (0.21mL, 0.6 mmol). After 1 h, the reaction mixture was quenched with methanol (0.12mL), diluted with saturated NH_4Cl (aq), and extracted with ethyl acetate. The combined organic phases were washed with saturated $CuSO_4$ (aq), water, and saturated NaCl (aq), and concentrated in vacuo. The resulting crude oil was dissolved in THF (6 mL), and Na_2HPO_4 (180 mg) and $Hg(O_2CCF_3)_2$ (180 mg, 0.42 mmol) were added. After 30 min at ambient temperature, the reaction mixture was quenched with saturated NH_4Cl (aq), and extracted with ethyl acetate. The combined organic phases were washed with saturated NH_4Cl (aq), and saturated NaCl (aq). Concentration in vacuo was followed by purification by preparative TLC (1 : 2 hexane/ethyl acetate). The resulting oil was dissolved in THF (1.5 mL), cooled to -20°C, and treated with HF•pyridine (25% HF in pyridine, prepared at -20°C, 0.3 mL). The reaction mixture was warmed to ambient temperature, stirred for 4 h, diluted with saturated NH_4Cl (aq), and extracted with ethyl acetate. The combined organic phases were washed with saturated NH_4Cl (aq), and saturated NaCl (aq). Purification by preparative TLC (10 : 1 CH_2Cl_2/methanol) afforded 13 mg (64%, 3 steps) of trihydroxy acid **138**.

$[\alpha]_D^{24}$ +34.4 (c 0.093, $CHCl_3$)

IR (neat) 3500, 3024, 1724, 1652, 1440, 1374, 1240, 1218 cm^{-1}

^{1}H NMR (250 MHz, C_6D_6) δ 1.07 (s, 3H), 1.13 (s, 3H), 1.24 (s, 9H), 1.43 (m, 5H), 1.71 (s, 3H), 1.73 (s, 3H), 1.98 (m, 3H), 2.42 (m, 3H), 2.91 (m, 8H), 3.21 (s, 3H), 3.35 (s, 3H), 3.38 (s, 3H), 3.44 (s, 3H), 3.63 (m, 1H), 3.88 (m, 4H), 4.20 (m, 1H), 4.27 (m, 1H), 4.42 (m, 1H), 5.51 (m, 2H), 5.53 (m, 1H), 5.73 (s, 1H), 5.79 (s, 1H), 6.29 (s, 1H), 6.41 (d, J = 16.4 Hz, 1H)

Preparation of Macrolactone 139 [Scheme 8-4 (cont.)]



138 **139**

To a refluxing solution of DCC (35 mg, 0.17 mmol), pyridine (0.33 mL, 8.2 mmol), and PPTS (43 mg, 0.17 mmol) in $ClCH_2CH_2Cl$ (8 mL) was add a solution of **138** (13 mg, 0.017 mmol) in $ClCH_2CH_2Cl$ (0.5mL) over a period of 5 h. The mixture was cooled to ambient temperature and methanol (2 mL) and AcOH (0.5 mL) were added. After an additional 30 min, the solution was diluted with ethyl acetate and the combined organic phases were washed with water, saturated $NaHCO_3$ (aq), and saturated NaCl (aq). Purification by preparative TLC (1 : 3 hexane/ethyl acetate) afforded 6.9 mg (51%) of desired macrolactone **139**.

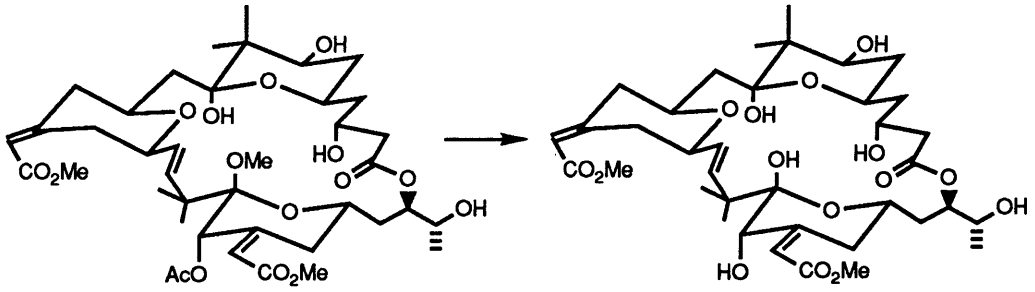
$[\alpha]_D^{24}$ +50.0 (c 0.028, $CHCl_3$)

IR (neat) 3432, 2932, 2856, 1724, 1644, 1236 cm^{-1}

^{1}HNMR (200 MHz, C_6D_6) δ 0.87 (d, J = 6.3 Hz, 3H), 1.00 (s, 3H), 1.09 (s, 3H), 1.15 (s, 3H), 1.28 (s, 3H), 1.33 (m, 8H), 1.72 (s, 1H), 1.74 (m, 1H), 2.05-2.28 (m, 6H), 3.06 (s, 3H), 3.23 (br. s, 3H), 3.26 (s, 3H), 3.27 (s, 3H), 3.50 (m, 1H), 3.82 (m, 2H), 4.14 (m, 1H), 4.35-4.44 (m, 3H), 4.54 (ddd, J = 11, 7.1, 2.6 Hz, 1H), 4.83 (d, J = 7.1 Hz, 1H), 4.89 (dd, J = 11.0, 4.8 Hz, 1H), 5.42 (m, 1H), 5.49 (s, 1H), 5.65 (dd, J = 16, 8.5 Hz, 1H), 5.83 (s, 1H), 6.31 (s, 1H), 6.50 (d, J = 16 Hz, 1H)

HRMS $[M-2MeOH]^+$ calculated : 732.3357, found 732.3354

Preparation of Hemiacetal 140 (Scheme 8-5)



139 **140**

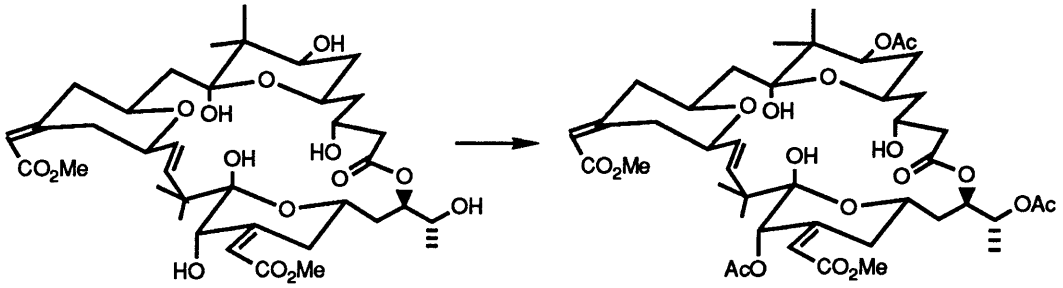
To a solution of acetate **139** (2.2 mg, 0.003 mmol) in anhydrous methanol (0.75 mL) was added anhydrous K_2CO_3 (2 mg). The reaction mixture was stirred for 2 h at ambient temperature and quenched with 5 % HCl (aq), stirred for 5 min, and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ (aq), saturated NaCl (aq), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparative TLC afforded 1.2 mg (54 %) of **140**.

IR (neat) 3468, 3020, 2936, 2860, 1714, 1660, 1218 cm^{-1}

^{1}H NMR (200 MHz, C_6D_6) δ 0.83 (s 3H), 1.04 (s, 3H), 1.06 (d, J = 6.1 Hz, 3H), 1.28 (s, 3H), 1.46 (s, 3H), 1.61 (m, 12H), 2.00 (m, 6H), 2.22 (m, 2H), 2.48 (m, 1H), 3.30 (s, 3H), 3.36 (s, 3H), 3.65-4.49 (m, 8H), 5.27 (m, 1H), 5.47 (s, 1H), 5.58 (dd, J = 15.7, 4.8 Hz, 1H), 5.74 (s, 1H), 5.87 (s, 1H), 6.19 (d, J = 15.7 Hz, 1H)

HRMS $[M-C_5H_{10}O]^+$ calculated : 654.2887, found 654.2889

Preparation of Triacetate 141 [Scheme 8-5 (cont.)]

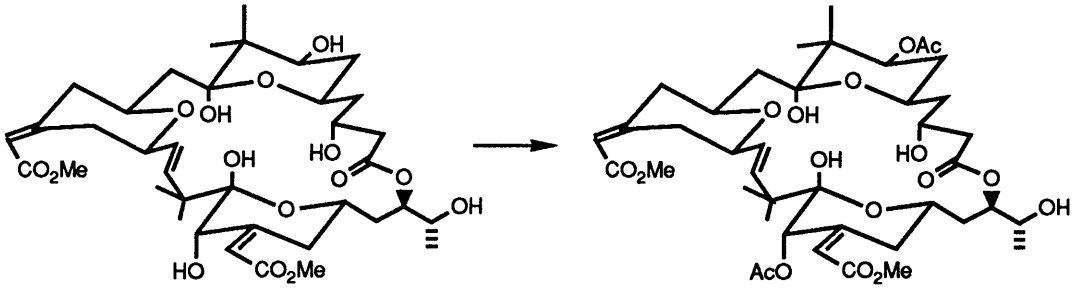


140 **141**

Triol **140** (0.60 mg, .00080 mmol) was dissolved in pyridine (0.15 mL) and Ac_2O (0.10 mL) was added. After stirring for 12 h at ambient temperature, the mixture was concentrated in vacuo, and diluted with water. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with saturated $NaHCO_3$ (aq) and saturated NaCl (aq), and were concentrated in vacuo. Purification by preparative TLC afforded 0.60 mg (99%) of triacetate **141** which proved to be identical (TLC and ^1H NMR) to that prepared in the same way from authentic bryostatin **7**.

^1H NMR (C_6D_6, 500 MHz) δ 0.87 (s, 3H), 0.91 (s, 3H), 1.03 (d, J = 6.3 Hz, 3H), 1.22 (s, 3H), 1.35 (s, 3H), 1.10-1.74 (m, 8H), 1.59 (s, 3H), 1.69 (s, 3H), 1.70 (s, 3H), 1.83 (br. t, 1H), 1.99 (m, 2H), 2.12 (br. d, 1H), 2.14 (s, 1H), 2.27 (d, J = 12 Hz, 1H), 2.32 (m, 1H), 3.21 (s, 3H), 3.35 (s, 3H), 3.57 (br. t, 1H), 3.75 (br. t, 1H), 4.06 (br. t, 1H), 4.17 (br. d, 1H), 4.29 (br. d, 1H), 4.35 (d, J = 12 Hz, 1H), 4.42 (br. t, 1H), 4.48 (br. t, 1H), 5.11 (q, J = 6.3 hz, 1H), 5.33 (dd, J = 12, 4.8 Hz, 1H), 5.54 (m, 1H), 5.54 (dd, J = 16, 8.6 Hz, 1H), 5.62 (s, 1H), 5.69 (s, 1H), 6.27 (d, J = 16 Hz, 1H), 6.40 (br. s, 1H), 5.70 (s, 1H).

Final Steps in the Preparation of Bryostatin 7 [Scheme 8-5 (cont.)]



140 **bryostatin7**

To a solution of triol **140** (1.2 mg, 0.0016 mmol) in DMF (100 μl) was added DMAP (one crystal), Et_3N (40 μl), and TBDM-Cl (10 mg, 0.067 mmol). The reaction mixture was stirred for 12 h at ambient temperature, quenched with water, extracted with ethyl acetate, washed with saturated NH_4Cl (aq), saturated $NaHCO_3$ (aq), and saturated NaCl (aq), and concentrated in vacuo. Purification by preparative TLC (1 : 4 hexane/EtOAc) afforded 0.60 mg (50%) of the monosilylated product which was dissolved in pyridine (0.15 mL) and Ac_2O (0.10 mL). After stirring for 12 h at ambient temperature, the mixture was concentrated in vacuo, and the residue was treated with 45% HF/CH_3CN (1 : 20, 0.2 mL) at 0°C. The reaction mixture was stirred for 2 h at 0°C, diluted with water, extracted with ethyl acetate, washed with saturated $NaHCO_3$ (aq) and saturated NaCl (aq), and concentrated in vacuo. Purification by preparative TLC afforded 0.5 mg (40%, 2 steps) of bryostatin **7**, identical with that of natural origin by TLC in several solvent systems, and ^1H NMR (500 MHz, C_6D_6) at varied concentrations.

References

1. Pettit, G.T.; Herald, C.L.; Doubek, D.L.; Herald, D.L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846.

2. Pettit, G.R.; Day, J.F.; Hartwell, J.L.; Wood, H.B. *Nature (London)* **1970**, *227*, 962.

3. Pettit, G.R.; Herald, D.L.; Gao, F.; Sengupta, D.; Herald, C.L. *J. Org. Chem.* **1991**, *56*, 1337.

4. Pettit, G.R.; Leet, J.E.; Herald, C.L.; Kamano, Y.; Boetter, F.E.; Baczynskyj, L.; Nieman, R.A. *J. Org. Chem.* **1987**, *52*, 2854.

5. For reports concerning the biosynthesis of aplasmomycin, a boron-containing antibiotic, see : Lee, J.J.; Dewick, P.M.; Gorst-Allman, C.P.; Spreafico, F.; Kowal, C.; Chang, C.-j.; McInnes, A.G.; Walter, J.A.; Keller, P.J.; Floss, H.G. *J. Am. Chem. Soc.* **1987**, *109*, 5426 and references cited therein.

6. Initial reports on bryostatins **2** through **13** are as follows. (a) **2** : Pettit, G.R.; Herald, C.L.; Kamano, Y.; Gust, D.; Aoyagi, R. *J. Nat. Prod.* **1983**, *46*, 528. (b) **3** : Petit, G.R.; Herald, C.L.; Kamano, Y. *J. Org. Chem* **1983**, *48*, 5354. (c) **4** : Pettit, G.R.; Kamano, Y.; Herald, C.L.; Tozawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6768. (d) **5-7** Pettit, G.R.; Kamano, Y.; Herald, C.L.; Tozawa, M. *Can. J. Chem.* **1985**, *63*, 1204. (e) **8** : Pettit, G.R.; Kamano, Y.; Aoyagi, R.; Herald, C.L.; Doubek, D.L.; Schmidt, J.M.; Rudloe, J.J. *Tetrahedron* **1985**, *41*, 985. (f) **9** : Pettit, G.R.; Kamano, Y.; Herald, C.L. *J. Nat. Prod.* **1986**, *49*, 661. (g) **10** and **11** : Pettit, G.R.; Kamano, Y.; Herald, C.L. *J. Org. Chem.* **1987**, *52*, 2848.

(h) **12** and **13** : Pettit, G.R.; Leet, J.E.; Herald, C.L.; Kamano, Y.; Boettner, F.E.; Baczynskyj, L.; Nieman, R.A. *Ibid.* **1987**, *52*, 2854. For a recent review on the isolation, characterization, and biological activity of the bryostatins, see: (i) Pettit, G.R. *The Chemist* **1989**, 11-21.

7. For a discussion of this method, in which sodium or silver salts are used to allow for consistant observation of $[M + Na]^+$ or $[M + Ag]^+$, see : Pettit, G.R.; Holzaptel, C.W.; Cragg, G.M.; Herald, C.L.; Williams, P. *J.Nat. Prod.* **1983**, *46*, 917.

8. The incorrect structure for bryostatin **3** was published in 1983 (Ref. 6b) and was reiterated several times in the literature before its correction in 1991 (Ref. 3).

9. (a) Jalava, A.M.; Heikkila, J.; Akerlind, G.; Pettit, G.R.; Akerman, K.E.O. *Cancer Research*, **1990**, *50*, 3422 and references cited therein. (b) Hennigs, H.; Robinson, V.A.; Michael, D.M.; Pettit, G.R.; Jung, R.; Yuspa, S.H. *Ibid.* **1990**, *50*, 4794 and references cited therein. (c) Lilly;, M.; Tompkins, C.; Brown, C.; Pettit, G.; Kraft, A. *Ibid.* **1990**, *50*, 5520 and references cited therein.

10. For example, see: (a) Trenn, G.; Pettit, G.R.; Takayama, H.; Hu-Li, J.; Sitkovsky, M.V. *J. Immunol.* **1988**, *140*, 433. (b) Mohr, H.; Pettit, G.R.; Plessing-Menze, A.; *Immunobiol.* **1987**, *175*, 420.

11. May, W.S.; Sharkis, S.J.; Esa, A.H.; Gebbia, V.; Kraft, A.S.; Pettit, G.R.; Sensenbrenner, L.L. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 8483.

12. (a) Smith, J.B.; Smith, L.; Pettit, G.R. *Biochem. Biophys. Res. Commun.* **1985**, *132*, 939. (b) Berkow, R.L.; Kraft, A.S. *Ibid.* **1985**, *131*, 1109. (c) Kraft, A.S.; Baka, V.V.; May, W.S. *Oncogene*, **1987**, *1*, 111.

13. Devries, D.J.; Herald, C.L.; Pettit, G.R.; Blumberg, P.M. *Biochem. Pharmocol.* **1988**, *37*, 4069.

14. (a) For a report on the use of vinyl radical cyclization methodology for the synthesis of a [C(10)-C(16)]-subunit, see : Munt, S.P.; Thomas, E.J. *J. Chem. Soc., Chem. Commun.* **1989**, 480. (b) For a report on the synthesis of an aldehydic [C(17)-C(20)]-subunit and a [C(21)-C(27)]-dithiane subunit see : Roy, R.; Rey, A.W.; Charron, M.; Molino, R. *J. Chem. Soc. Chem. Commun.* **1989**, 1308. (c) For a general method applied to the 1,3-anti array of alcoholic moieties found in the completely acyclic form of bryostatins, see : Evans, D.A.; Gauchet-Prunet J.A.; Carreira, E.M.; Charett, A.B. *J. Org. Chem.* **1991**, *56*, 741.

15. For leading references on macrolactonization in the total synthesis of complex natural products, see: (a) Paterson, I.; Mansuri, M.M. *Tetrahedron* **1985**, *41*, 3569. (b) Boeckman, R.K., Jr.; Goldstein, S.W. In *The Total Synthesis of Natural Products;* Apsimon, J., Ed.; Wiley: New York, 1988; Vol. 7, pp 1-139.

16. (a) For the original work in this area, see : Masamune, S.; Bates, G.S.; Corcoran, J.W. *Angew. Chem. Int. Eng. Ed.* **1977**, *16*, 585. (b) For further developments, see : Nicolaou, K.C.; Daines, R. A.; Chadraborty, T.K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685 and references cited therein.

17. Corey, E.J.; Gilman, B.E.; Ganem, B.E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

18. Hanessian, S.; Lavallee, P.; *Can. J. Chem.* **1975**, *53*, 2975.

19. Hart, T.W.; Metcalfe, D.A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156.

20. (a) Julia, M.; Paris, J.-M. *Tetahedron Lett.* **1973**, 4833, 4836. (b) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763. (c) For a recent review, see: Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97.

21. (a) For the initial report see: Masamune, S.; Sato, T.; Kim, B.-M.; Wollman, T.A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (b) For further discussion, including the use of other chiral boron reagents with achiral methyl ketones, see: Kim, B.-M.; PhD Thesis, MIT, 1987.

22. Pougny, J.-R.; Nassr, M.A.M.; Sinay, P. *J. Chem Soc., Chem Commun.* **1981**, 375.

23. For initial reports on the MPM- and DMPM-protecting groups see: (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885. (b) Oikawa, Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5393. (c) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397. (d) For a review see: Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

24. For numerous examples of asymmetric 1,2-induction see: (a) Reetz, M.T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556. (b) Sato, F.; Takahashi, O.; Kato, T.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 1638. (c) Mead, K.; MacDonald, T.L. *J. Org.*

Chem. **1985**, *50*, 422. (d) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Taketoda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636. (e) Lipshutz, B.H.; Wilhelm, R.S.; Koslowski, J.A. *Tetrahedron* **1984**, *40*, 5005.

25. For a more comprehensive discussion of double asymmetric synthesis, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.

26. Many examples are given in Ref. 25. For examples of D.A.S. with the acetate aldol reaction other than those reported in this thesis, see : (a) Short, R.P; Masamune, S. *Tetrahedron Lett.* **1987**, *28*, 2841. (b) Duplantier, A.J.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7079.

27. For examples of internal chiral reagents that display significant selectivity in the acetate aldol reaction, see : (a) Davies, S.G.; Dordor, I.M.; Warner, P. *J. Chem. Soc., Chem. Commun.* **1984**, 956. (b) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031.

28. For a study of external reagents that display modest selectivity with methyl ketone aldol reactions, see Ref. 21a.

29. (a) For the initial report on this methodology see: Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. b) For a landmark application see: Reed III, L.A.; Ito, Y.; Masamune, S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1982**, *104*, 6468. c) For a complete report of the experiments summarized in Ref. 19b see: Soo, Y.K.; Lee, A.W.M.; Masamune, S.; Reed III, L.A.; Sharpless, K.B.; Walker, F.J.; *Tetrahedron*, **1990**, *46*, 245.

30. Mancuso, A.J.; Swern, D. *Synthesis*, **1981**, 165.

31. Wadsworth, W.S.; Emmons, W.D. *Org. Syntheses* **1965**, *45*, 44.

32. Aldehyde **56** was prepared from cis-3-hexen-1-ol in two steps which is reported in the experimentals (Chapter 9). Its use was described on one occasion prior to this work: Roush, W.R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

33. Dale, J.A.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

34. (a) Kluge, A.F.; Untch, K.G.; Fried, J.H. *J. Am. Chem. Soc.* **1972**, *94*, 782. (b) Stork, G.; Takahashi, T. *Ibid.* **1977**, *99*, 1275. (c) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1976**, 276.

35. For a study that exploits the tendancy of β-alkoxythioesters to spontaneously lactonize under basic conditions, see : Danheiser, R.L.; Nowick, J.S. *J. Org. Chem.* **1991**, *56*, 1176.

36. For the conversion of *tert*-butylthioesters to methyl ketones with lithium dimethylcuprate see: McGarvey, G.J.; Williams, J.M.; Hiner, R.N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943.

37. The preparation of aldehyde **62** from 2,2-dimethyl-1,3-propanediol in two or three steps has been described several times; for example, see: Yeh, C.-L. Dawson, M.; Hemler, M.E.; Lands, W.E.M. *Tetrahedron Lett.* **1977**, 4257.

38. (a) Saksena, A.K.; Mangiaraeina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Evans, D.A.; Chapman, K.T. *ibid.* **1986**, *27*, 5939. (c) Evans, D.A.; Dimare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476.

39. Sulfone alkylation in this instance was, in itself, an accomplishment since the resulting β-alkoxysulfone might be expected to eliminate under the reaction conditions.

40. This oxidative removal of the sulfone moiety has worked well in some instances. See, for example : Little, R.D.; Myong, S.O. *Tetrahedron Lett.* **1980**, *21*, 3339.

41. Whritenour, D.C.; Ph.D. Thesis, MIT, 1988.

42. The preparation of THP-ether **70** has been described previously; for example, see: Jones, E.R.K.; Shen, T.J.; Whiting, M.C. *J. Chem. Soc., Chem Commun.* **1950**, 230.

43. (a) For the original report of this type of propargylic alcohol reduction, see: Corey, E.J.; Katsenellenbogen, J.A.; Posner, G.H. *J. Am. Chem. Soc.* **1967**, *89*, 4245. (b) For the use of Redal in this reaction, see: Denmark, S.E.; Jones, T.K. *J. Org. Chem.* **1982**, *47*, 4595.

44. Although this reaction was generally performed at 0°C, and was complete in less than 15 min, stirring the reaction mixture at ambient temperature did not decrease the yield or the purity of the aldehyde obtained.

45. Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559.

46. The 2,5-*trans*-dimethylborolanyl chloride (**77**) was first synthesized by Dr. Byong-Moon Kim (Ref. 21b) for direct use in aldol reaction.

47. Whitesides, G. M.; Hill, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 870.

48. For reports on (oxygen) nucleophilic epoxide ring-opening reactions, see: (a) Corey, E.J.; Hopkins, P.B.; Muroe, J.E.; Marfat, A.; Hashimoto, S. *J. Amer. Chem. Soc.* **1980**, *102*, 7986. (b) Ref. 19b. (c) Minami, N.; Ko, S.; Kishi, Y. *J. Amer. Chem. Soc.* **1982**, *104*, 1109. (d) Roush, W.R.; Brown, R.J.; Dimare, M. *J.Org. Chem.* **1983**, *48*, 5083.

49. Propargylic and allenyl anions have been only rarely used in this capacity. See : Danheiser, R.L.; Carini, D.; Kwasigroch, C.A. *J. Org. Chem.* **1986**, *51*, 3870.

50. Piers, E.; Chong, J.M.; Morton, H.E. *Tetrahedron Lett.* **1981**, *22*, 4905.

51. Small nucleophiles, e.g. methyl or vinyl, have provided excellent (>20:1) selectivity. See Ref. 24.

52. (a) Burgi, H.B.; Dunitz, J.D.; Shefter, E.J. *J. Amer. Chem. Soc.* **1973**, *95*, 5065. (b) Lodge, E.P.; Heathcock, C.H. *J. Amer. Chem. Soc.* **1987**, *109*, 2819.

53. This molybdenum compound was a precursor in the preparation of MoOPh : Vedejs, E.; Engler, D.A.; Telschow, J.E. *J. Org. Chem.* **1978**, *43*, 188.

54. This molybenum reagent reacted with sulfide **102** to rapidly provide the corresponding sulfoxide.

55. Tsunoda, T.; Susuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

56. Similar problems have been encountered. See, forexample: Evans, D.A.; Kaldor, S.W.; Jones, T.K.; Clardy, J.; Stout, T.J. *J. Am. Chem. Soc.* **1990**, *112*, 7001 and references cited therein.

57. For another example of this problem see: Gais, H.-J.; Ball, W.A.; Bund, J. *Tetrahedron Lett.* **1988**, *29*, 781.

58. (a) For a general discussion, see Ref 16a. For specific examples, see : (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk.A.; Garvey, D.S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. (c) Park, P.; Broka, C.A.; Johnson, B.F.; Kishi, Y. *Ibid.* **1987**, *109*, 6205.

59. Zimmerman, H.E.; Traxler, M.D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

60. The several constituents of this complex mixture could not be assigned unambiguous structures because of their inseparability.

61. The selectivity of aldehyde **126** in the aldol reaction has been examined for several achiral boron enolates. For example, see Ref. 26a.

62. For analysies of related diastereomeric mixtures, see Refs. 26a and 58b.

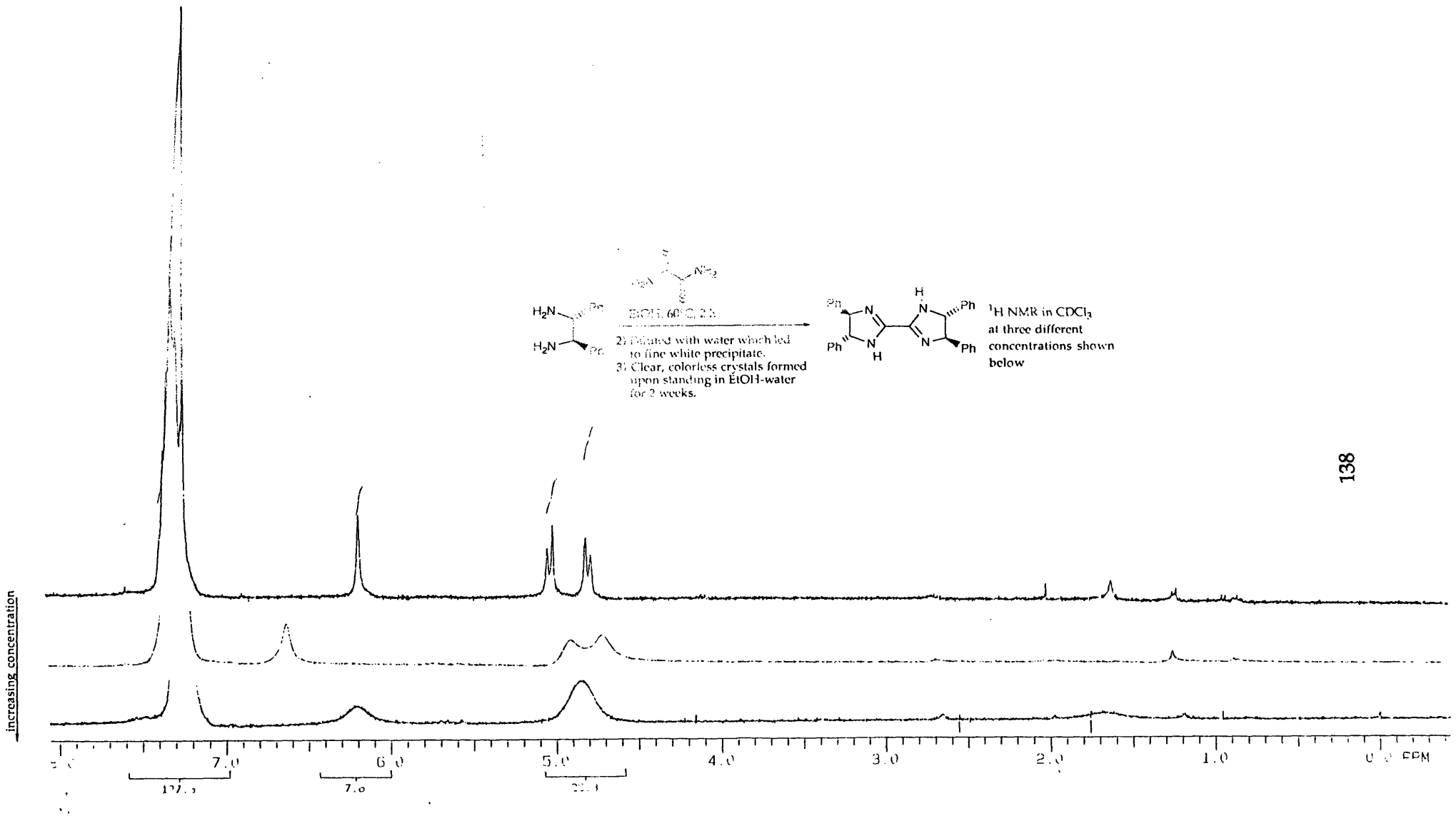
63. For the reaction of β-hydroxy carboxylic acid thiol esters, see (a) Masamune, S.; Hayase, Y.; Chan, W.K.; Sobczak, R.L. *J. Am. Chem. Soc.* **1976**, *98*, 7874. (b) Masamune, S; Lu, L.D.-L.; Jackson, W.P.; Kaiho, T.; Toyoda, T. *Ibid* **1982**, *104*, 5523.

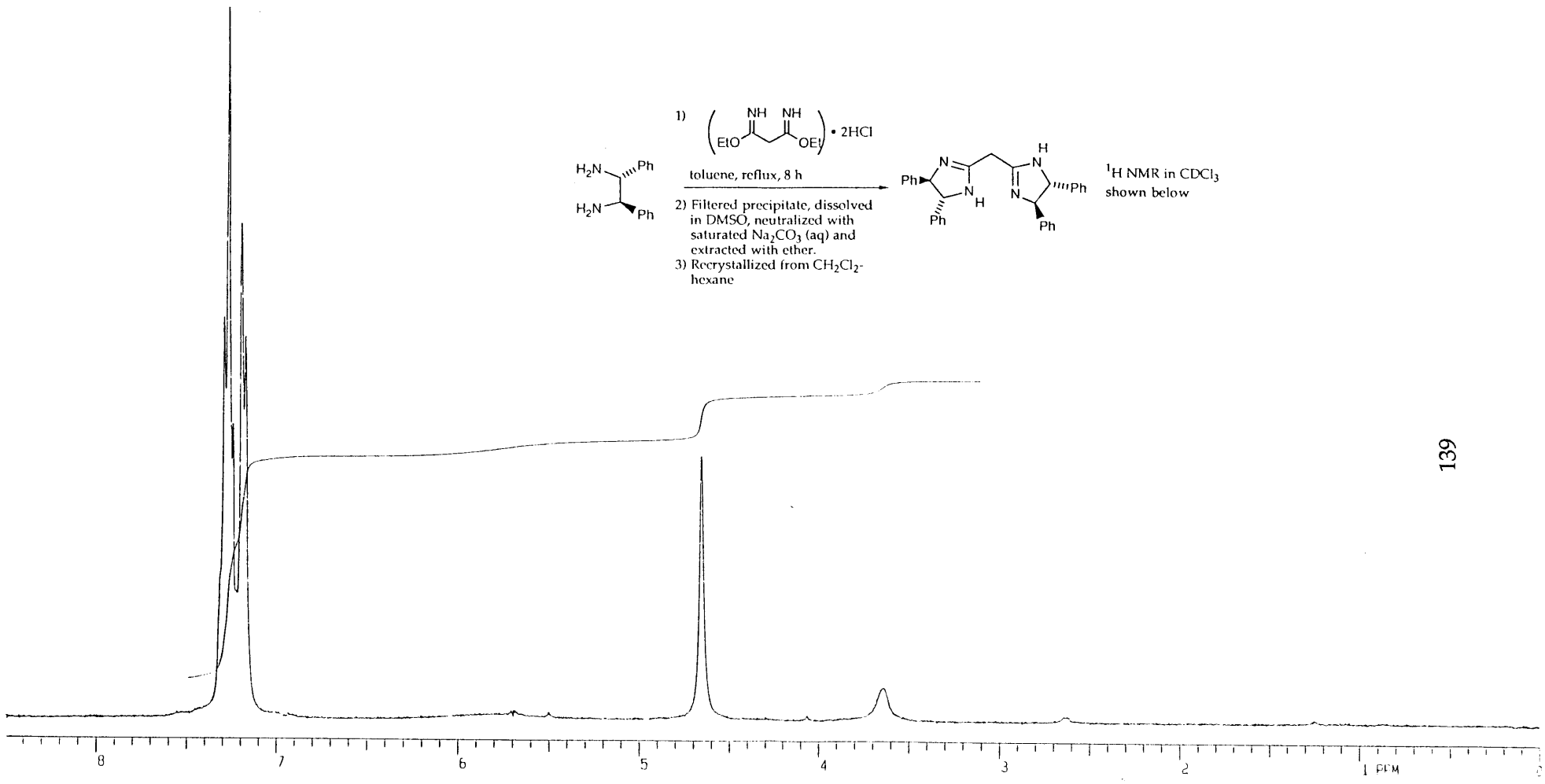
64. (a) Haslam, E. *Tetrahedron* **1980**, *36*, 2409. (b) Boden, E.P.; Keck, G.E. *J. Org. Chem.* **1985**, *50*, 2394. Use of DMAP hydrochloride (instead of pyridine and PPTS) led to an intractable mixture.

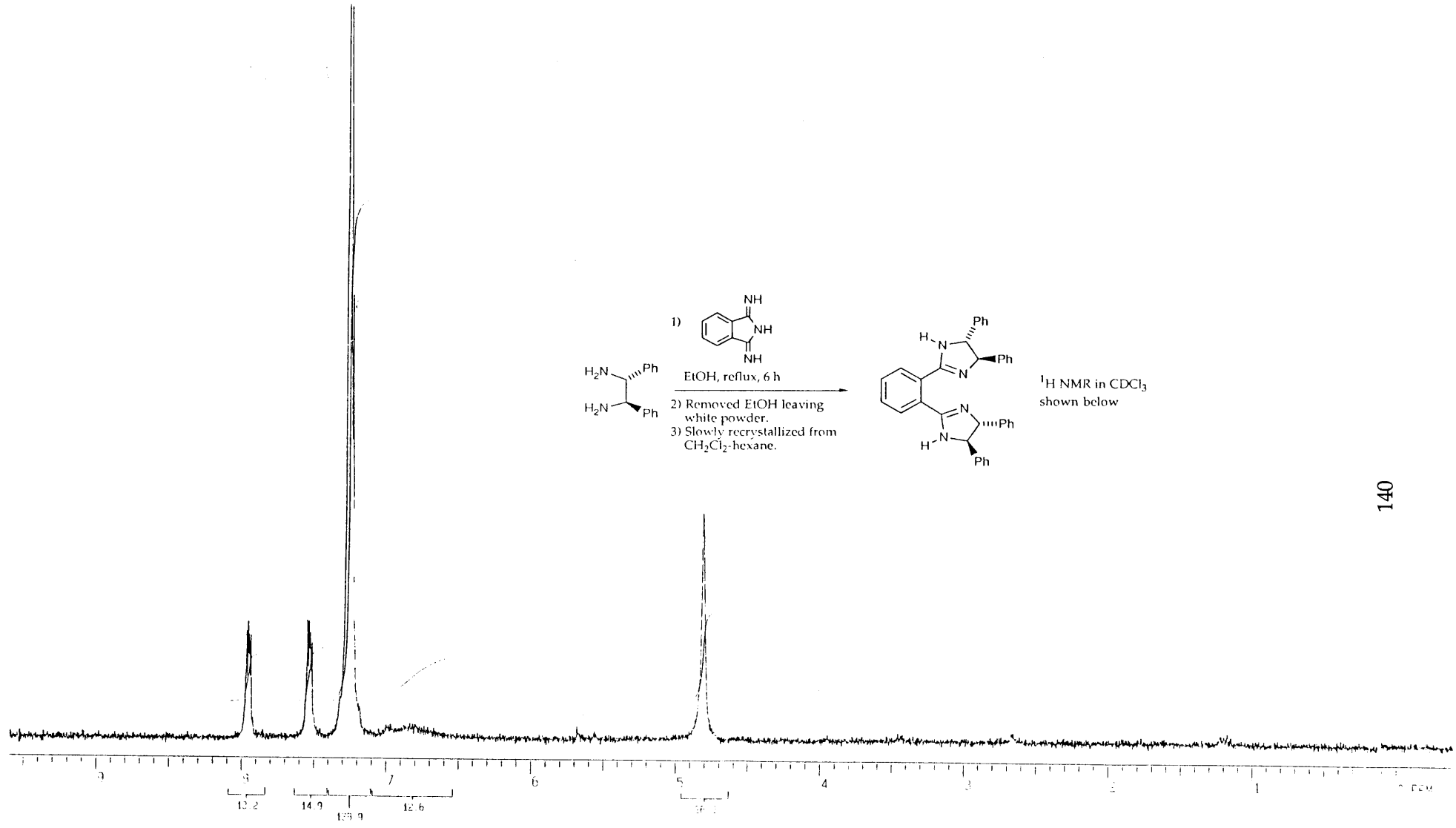
65. For this similar observation see, inter alia: Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 7530.

Appendix I : Synthesis of Bisimidazolines

As part of a project involving the application of novel chiral ligands to metal-mediated catalytic processes, bisimidazolines were prepared. Synthesis of the diphenyl bisimidazolines illustrated in the next three pages proved not to be feasible via the methodology already known for their parent compounds (where Ph=H). Reaction schemes and reproductions of ^1H NMR spectra are provided.

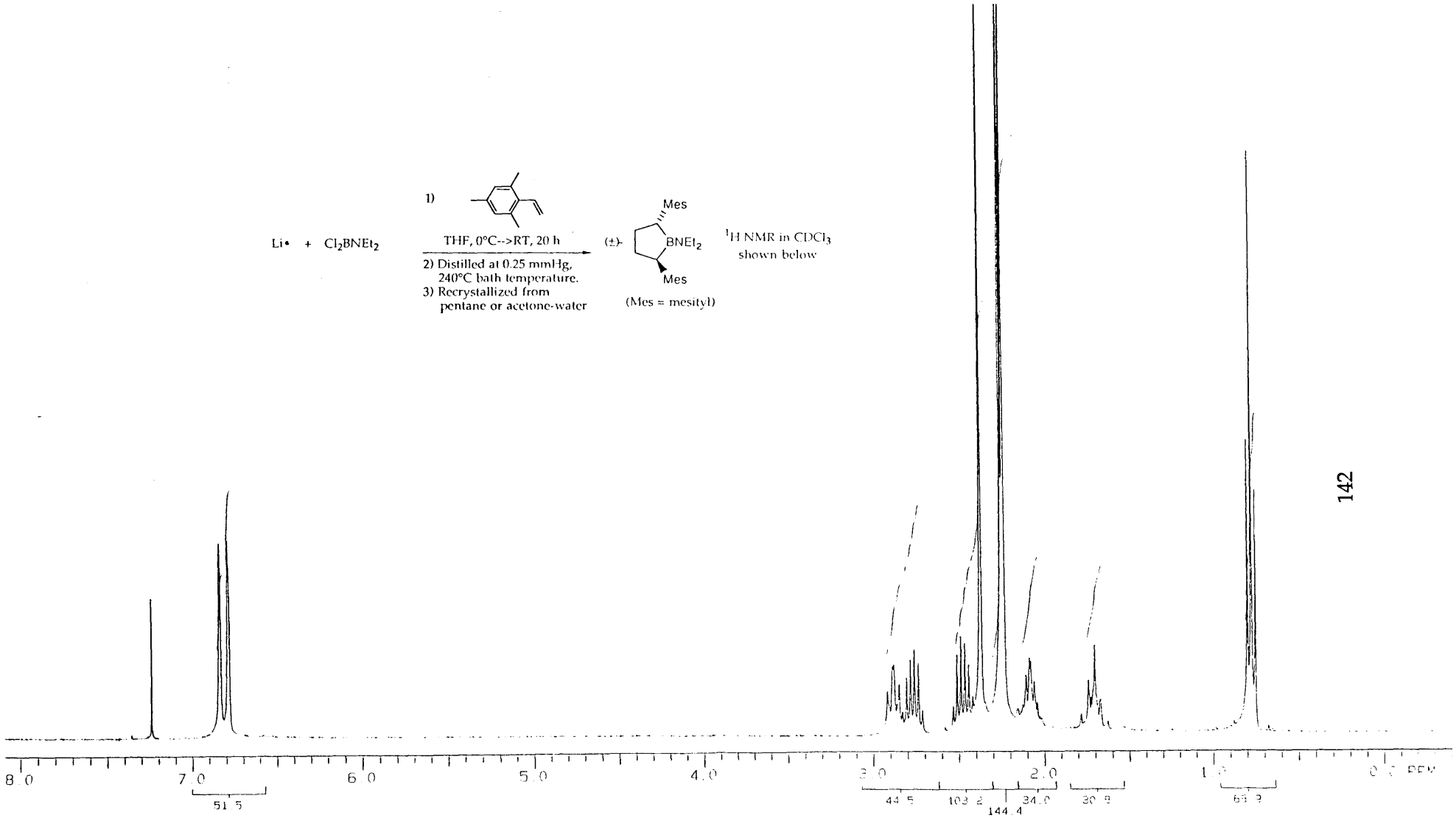

2) Diluted with water which led to fine white precipitate.
3) Clear, colorless crystals formed upon standing in EtOH-water for 2 weeks.
^{1}H NMR in $CDCl_3$ at three different concentrations shown below
increasing concentration
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

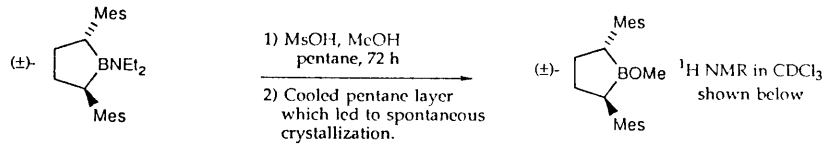

1)
NH NH
EtO OEt
• 2HCl
toluene, reflux, 8 h
2) Filtered precipitate, dissolved in DMSO, neutralized with saturated Na_2CO_3 (aq) and extracted with ether.
3) Recrystallized from CH_2Cl_2-hexane
^1H NMR in $CDCl_3$ shown below
8
7
6
5
4
3
2
1 PPM


1)
EtOH, reflux, 6 h
2) Removed EtOH leaving white powder.
3) Slowly recrystallized from CH_2Cl_2-hexane.
^{1}H NMR in $CDCl_3$ shown below

Appendix II : Preliminary Studies on 2,5-*Trans*-Dimesitylborolanyl derivatives

As part of a study of chiral reagents that contain the 2,5-*trans*-dialkylborolanyl moiety, the title compounds were examined. The synthesis of a variety of derivatives is illustrated in the next nine pages with reaction schemes and reproductions of ^1H NMR spectra.

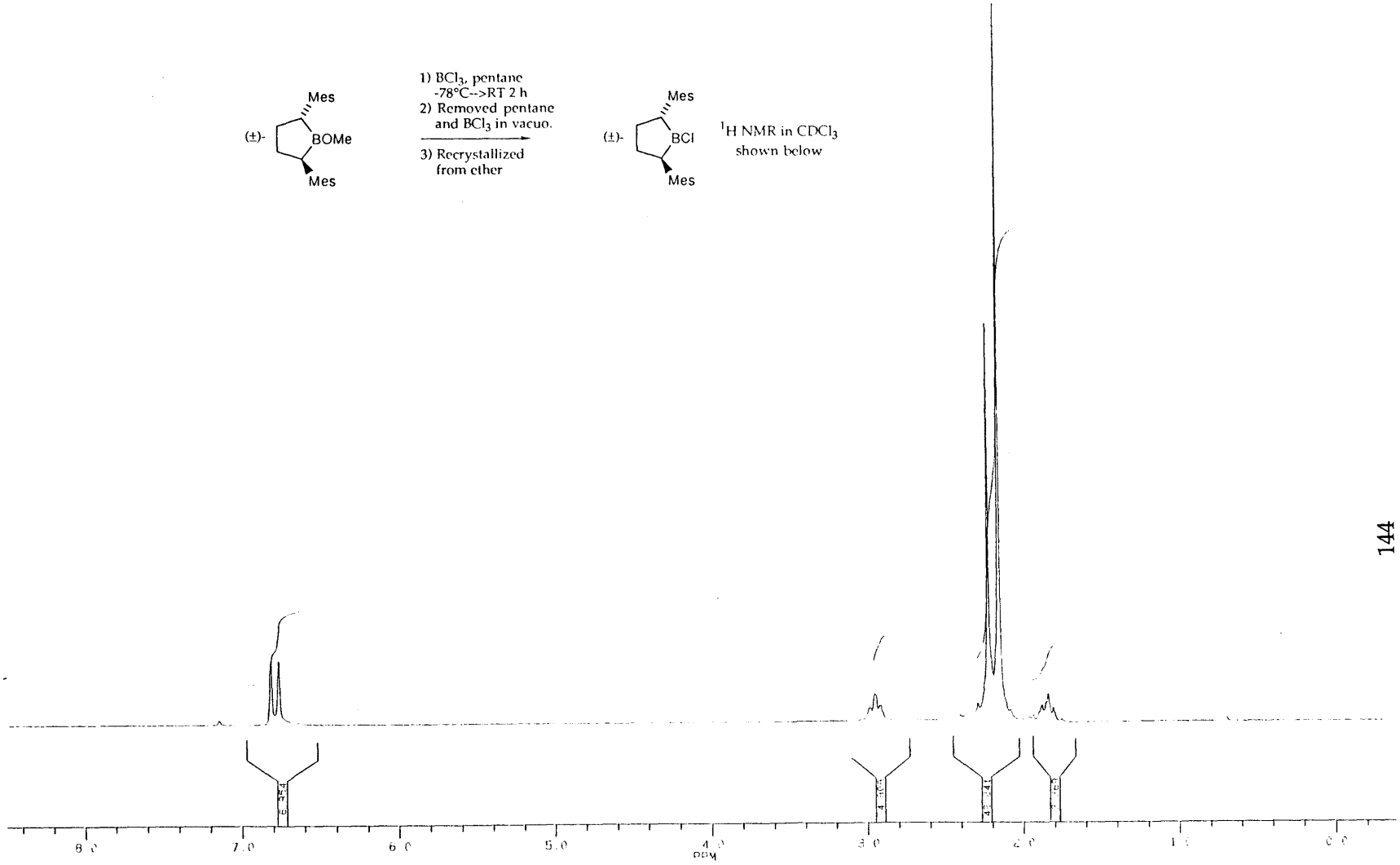

Li• + Cl2BNEt2
1)
THF, 0°C-->RT, 20 h
2) Distilled at 0.25 mmHg, 240°C bath temperature.
3) Recrystallized from pentane or acetone-water
(±)-
Mes
BNEt2
Mes
(Mes = mesityl)
1H NMR in CDCl3 shown below
142
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
51.5
44.5
103.2
34.0
144.4
30.8
68.9

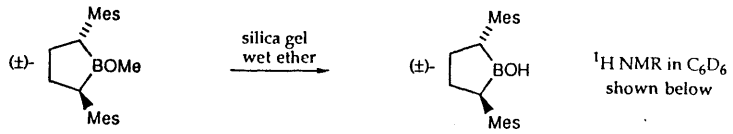


1) MsOH, MeOH
pentane, 72 h

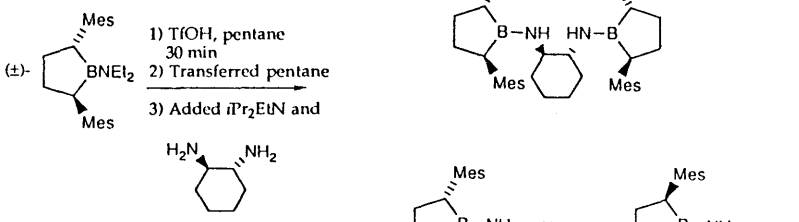
2) Cooled pentane layer which led to spontaneous crystallization.

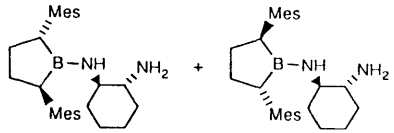
^{1}H NMR in $CDCl_3$ shown below


Mes
(±)-
BOMe
Mes
1) BCl_3, pentane
-78°C-->RT 2 h
2) Removed pentane
and BCl_3 in vacuo.
3) Recrystallized
from ether
Mes
(±)-
BCl
Mes
^1H NMR in $CDCl_3$
shown below
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

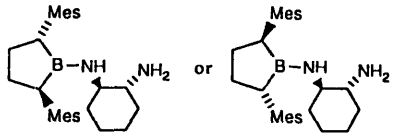


^{1}H NMR in C_6D_6
shown below

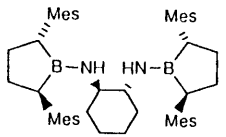




Diastereomers are separable by silica gel chromatography and can be reconverted to the triflate with 3 eq of TfOH. ^{1}H NMR of the higher R_f diastereomer in $CDCl_3$ is shown below.



^{1}H NMR of the lower R_f diastereomer in $CDCl_3$ is shown below



This structure that contains one *R,R*-borolanyl moiety and one *S,S*-borolanyl moiety is consistent with i) the ^{13}C NMR spectrum, ii) conversion to other diastereomeric derivatives, and iii) the ^{1}H NMR shown below.

Appendix III : Publications

Reproductions of the articles listed below are given in the 19 pages that follow:

1. "$KMnO_4$ Revisited : Oxidation of Aldehydes to Carboxylic Acids in the *tert*-Butyl Alcohol-Aqueous Na_2PO_4 System"

2. "Synthesis of Bryostatins. 1. Construction of the C(1)-C(16) Fragment"

3. "Triple Asymmetric Synthesis for Fragment Assembly: Validity of Approximate Multiplicativity of the Three Diastereofacial selectivities"

4. "Synthesis of Bryostatin 7"

Tetrahedron Letters,Vol.27,No.38,pp 4537-4540,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

$KMnO_4$ REVISITED: OXIDATION OF ALDEHYDES TO CARBOXYLIC ACIDS IN THE *tert*-BUTYL ALCOHOL - AQUEOUS NaH_2PO_4 SYSTEM

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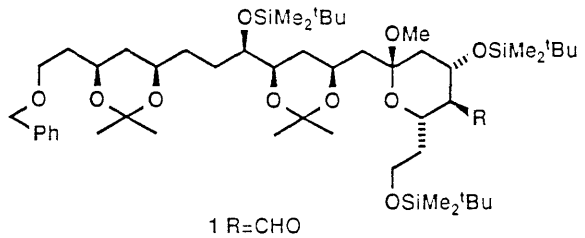
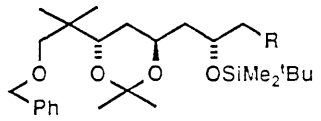
Abstract: Aldehydic compounds with one or more protected hydroxyl groups are effectively oxidized with $KMnO_4$ to the corresponding carboxylic acids using a mixture of *t*-BuOH and aqueous NaH_2PO_4 as a reaction medium.

Several oxidants are commonly used to convert aldehydes to carboxylic acids.[1] This seemingly simple conversion, however, is by no means straightforward with a highly oxygenated system such as 1, and a variety of side reactions concurrently take place. For instance, reaction of 1 with either the Jones reagent or $RuCl_3(H_2O)_n$-$NaIO_4$[2] provides a complex mixture of products apparently differing in the oxidation state and site, and



1 R=CHO

2 R=COOH



3 R=CHO

4 R=COOH

the yields of the corresponding carboxylic acid 2[3] are less than 20% in both cases. On the other hand, 1 slowly decomposes into an uncharacterized product with AgO.[4] Pressed by the need for an oxidant capable of achieving a "clean" conversion of 1 to 2 as well as 3 to 4,[3] we have examined the reaction conditions commonly used for several reagents, in particular $KMnO_4$. As outlined below, the simple selection of a *t*-BuOH-aqueous NaH_2PO_4 mixture as a reaction medium may render this reagent, $KMnO_4$, widely applicable in the synthesis of complex natural products. This modification is devised in light of the observation that the $KMnO_4$ oxidation of aliphatic aldehydes shows general-acid catalysis over the pH range 2.80-6.86.[5]

A set of experiments was carried out first to define a standard procedure for this oxidation using the aldehyde 5 as a substrate. Thus, a solution of 5 (0.5 mmol) in *t*-BuOH (3 mL) was diluted with an aqueous 1.25 M potassium phosphate buffer solution (2 mL) adjusted to a certain pH value and to the resulting solution was added, with vigorous stirring, an aqueous 1 M $KMnO_4$ solution (3.0 mL) at room temperature.

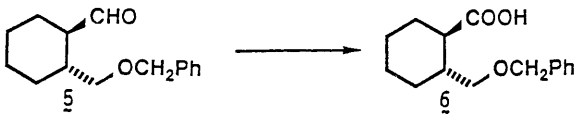


Table 1 Oxidation of aldehyde 5 to carboxylic acid 6[a]

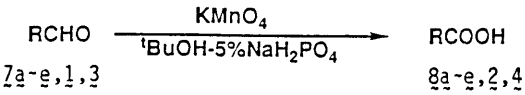
entry	pH of buffer added	reaction time	yield of 6 (%)	recovered 5 (%)
1	2.0	20 min [e]	43	45
2	3.7	10 min	95	
3	4.4[b]	2 min	95	
4	5.0	2 min	95	
5	6.0	2 min	96	
6	7.0	2 min	96	
7	10.0	10 min	91	
8	12.0	40 min [e]	90	5
9	c	6 min	86	
10	d	4 h	38	56

[a] See the text for the reaction conditions. [b] 5% NaH_2PO_4 (2 mL) used. [c] H_2O used instead of a phosphate buffer solution. [d] Solid $KMnO_4$ added. [e] All of the $KMnO_4$ consumed by the end of the specified reaction time.

After a certain reaction time, the oxidation was quenched by the addition of a saturated solution of Na_2SO_3 and the resulting pH of the mixture was adjusted to 3 with cold (0°C) dilute HCl to dissolve the colloidal MnO_2. The usual extractive workup followed by flash chromatography on silica gel provided the carboxylic acid 6, and in some cases with recovered 5.

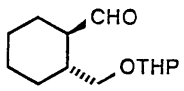
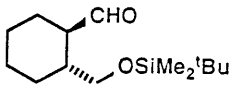
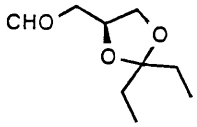
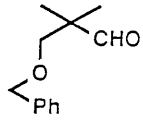
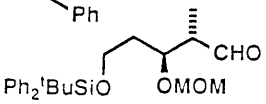
Table 1 summarizes the results. With a buffer solution of pH 4.4, 5.0, 6.0, or 7.0, the oxidation of 5 to 6 is brought to completion in excellent yields (entries 3 -6). In the pH 2 and 12 experiments (entries 1 and 7) $KMnO_4$ auto-decomposes rapidly, the aldehyde 5 being partially recovered. Note the amount of the phosphate used in the oxidation is small, yet is still sufficient to prevent the hydroxide produced from causing deleterious effects. In the absence of water, the oxidation proceeds much more slowly[6] (entry 9), and this result may be compared with three known procedures as applied to the conversion of 5 to 6: (1) $KMnO_4$ (1 equiv) and dicyclohexyl-18-crown-6 in benzene (reaction conditions, 36 h at room temperature),[7] yield of 6, 46% and recovery of 5, 42%; (2) Bu_4NMnO_4 (2-3 equiv) in pyridine (2 h at room temperature),[8] 6, 73% and 5, 17%; (3) $NaMnO_4.H_2O$ (5 equiv) in hexane (3 h under reflux),[9] 6, 29% and 5, 63%.

In a second set of experiments we have examined the extent to which various protected hydroxyl groups survive under the conditions specified in Table 1, entry 3, which appeared most suitable for this purpose. The substrates are 7a-e, 1 and 3. As Table 2 indicates, the aldehydes having an acetonide, benzyl ether,[10] tetrahydropyranyl ether, methoxymethyl



7a-e,1,3 8a-e,2,4

Table 2 Oxidation of aldehydes 7a-e, 1, and 3 to the corresponding carboxylic acids[a]

entry	substrate		reaction time (min)	yield (%)
1		7a	10	98
2		7b	10	95
3		7c	10	98
4		7d	10	99
5		7e	5	98
6	3		5	97
7	1		40	80-85

[a] Conditions specified in Table 1, entry 3.

ether and/or silyl ether are smoothly and rapidly converted to the corresponding carboxylic acids (entries 1 -5). Thus, through this modified version of $KMnO_4$ oxidation the synthetic intermediates 2 and 4 described in the introduction are now in our possession.[11]

A variety of reliable oxidizing reagents for the conversion of "sensitive" alcohols to aldehydes or ketones are available, but for the oxidation of "sensitive" aldehydes to carboxylic acids there are only a few. In view of its operational simplicity, efficiency, and selectivity, the modified method described above will hopefully prove to be of wide synthetic utility.

Acknowledgements. We thank the National Institutes of Health (CA 37804) for financial support.

References and Footnotes

(1) For leading reference books on the subject of oxidation, see (a) Chinn, L.J. "Selection of Oxidant in Synthesis," Mercel Dekker Inc. New York, 1971. (b) Wiberg, K.B. "Oxidation in Organic Chemistry," Academic Press, New York and London, 1965. For newer methods, see (c) PDC: Corey, E.J.; Schmidt, G. Tetrahedron Lett. 1979, 399. (d) 2-Hydroperoxyhexafluoro-2-propanol: Ganem, B.; Heggs, R.P.; Biloski, A.J.; Schwartz, D.R. Tetrahedron Lett. 1980, 21, 685. (e) Ozone: Sundararaman, P.; Walker, E.C.; Djerassi, C. Tetrahedron Lett. 1979, 1627. (f) Calcium hypochlorite: Nwaukwa, S.O.; Keehn, P.M. Tetrahedron Lett. 1982, 23, 3131. (g) Sodium Chlorite-H_2O_2: Dalcanale, E.; Montanari, F. J. Org. Chem. 1986, 51, 567 and references cited therein.

(2) (a) Rossiter, B.E.; Katsuki, T.; Sharpless, K.B. J. Am. Chem. Soc. 1981, 103, 464, footnote 15. (b) Carlsen, P.-H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. J. Org. Chem. 1981, 46, 3936.

(3) Compounds 2 and 4 are intermediates designed for syntheses of amphotericin B (Ganis, P.; Avitabile, G.; Mechlinski, W.; Schaffner, C.P. J. Am. Chem. Soc. 1971, 93, 4560) and bryostatin 1 (Petit, G.R.; Herald, C.L.; Doubek, D.L.; Herald, D.L.; Arnold, E.; Clardy, J. Ibid. 1982, 104, 6846), respectively.

(4) For instance, see (a) Corey, E.J.; Gilman, N.W.; Ganem, B.E. J. Am. Chem. Soc. 1968, 90, 5616. (b) Clarke, T.G.; Hampson, N.A.; Lee, J.B.; Morley, J.R.; Scanlon, B. Tetrahedron Lett. 1968, 5685.

(5) Freeman, F.; Lin, D.K.; Moore, G.R. J. Org. Chem. 1982, 47, 56 and references cited therein.

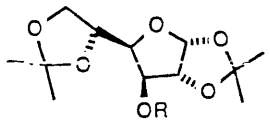
(6) (a) Menger, F.M.; Lee, C. J. Org. Chem. 1979, 44, 3446. See also (b) Nourelin, N.A.; Lee, D.G. J. Org. Chem. 1982, 47, 2790 and references cited therein.

(7) Sam, D.J.; Simmons, H.E. J. Am. Chem. Soc. 1972, 94, 4024.

(8) Sala, T.; Sargent, M.V. J. Chem. Soc. Chem. Commun. 1978, 253.

(9) Menter, F.M.; Lee, C. Tetrahedron Lett. 1981, 22, 1655.

(10) Benzyl ethers are slowly oxidized, e.g., three hours' exposure of 9 to this $KMnO_4$-NaH_2PO_4 at room temperature led to the formation of the cleavage product 10 (24%) with the recovery of 9 (76%).



9: R=CH_2Ph

10: R=H

(11) ^1H NMR spectra of 2 (400MHz, $CDCl_3$); δ -0.01(s, 3H), 0.035(s, 3H), 0.044(s, 3H), 0.05(s, 6H), 0.07(s, 3H), 0.84(s, 9H), 0.87(s, 18H), 1.16(m, 1H), 1.26-1.45(m, 3H) 1.32(s, 3H), 1.36(s, 3H), 1.40(s, 3H), 1.41(s, 3H), 1.46-1.55(m, 4H), 1.64(dd, J=6.0 and 14.4 Hz, 1H), 1.70-1.82(m, 4H), 1.90(br d, J=14.4 Hz, 1H), 2.21(dd, J=4.8 and 13.6 Hz, 1H), 2.32(t, J=10.2 Hz, 1H), 3.08(s, 3H), 3.40(m, 1H), 3.46-3.62(m, 3H), 3.66-3.86(m, 4H), 3.92(m, 1H), 4.03(m, 1H), 4.29(dt, J=4.8 and 10.2 Hz, 1H), 4.50(ABq, J_{AB}=12.3 Hz, 2H), 7.31(m, 5H), -10.0(br, 1H).

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Synthesis of Bryostatins. 1. Construction of the C(1)-C(16) Fragment†

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The synthesis of fragment AB [C(1)–C(16)] of bryostatin 1 is described. Two aldol coupling reactions involving (i) chiral fragment A [C(1)–C(10)] with achiral B [C(11)–C(16)] and (ii) chiral fragment A1 [C(7)–C(10)] with achiral A2 [C(6)–C(1)] constitute crucial steps in which an external chiral boron reagent is used to control stereoselectivity in the creation of a new stereogenic center. This type of double asymmetric synthesis, although rarely precedented, provides a powerful means of stereocontrol over the fragment assembly.

Two decades ago, Pettit et al. found that extracts from the invertebrate colonial filter-feeder *Bugula neritina* were active against the murine P388 lymphocytic leukemia.[1] Subsequent efforts directed toward the isolation of the bioactive constituents have yielded 13 bryostatins of known structure, all but one of which differ only in their C(7) and C(20) substituents.[2] Whereas bryostatin 1 (1),[2a] the most abundant bryostatin, contains C(7) acetate and C(20) octadienoate substituents, there are various other ester derivatives, as well as three C(20)-deoxy bryostatins. Because of their attractive stereostructural features, anticancer properties, and relative scarcity, we have chosen 1 as a synthetic target. As depicted in Scheme I, a logical (and straightforward) retrosynthesis of 1 begins with the dissection of the lactonic linkage and the C(16)–C(17) double bond to provide the two major fragments AB [C(1)–C(16)] and CD [C(17)–C(27)]. The AB fragment can be further disassembled into fragments A [C(1)–C(10)] and B [C(11)–C(16)] and finally into A1 [C(7)–C(10)] and A2 [C(1)–C(6)]. In the coupling of A1 and A2, a stereogenic center is created at C(7) of A, and in the coupling of A and B, at C(11) of AB. Thus, these reactions are concerned with a fundamental, general problem of convergent synthesis, which involves the stereoselective assembly of two fragments (at least one of which is chiral) with concomitant creation of a new stereogenic center or centers.[3]

Stereogenic centers embedded in fragments generally correspond directly to those of a target molecule. When a center (or centers) is/are created in the coupling of two fragments, e.g. an enolate and an aldehyde, the product ratio heavily depends on the diastereoselectivities[3a] of the two reactants. The stereoselection attained in such a coupling, once a choice of fragments has been made, is therefore predetermined and normally unpredictable in both magnitude and sense. Thus, the fragment-coupling step often constitutes the least stereoselective step in the total synthesis, and, traditionally, such a reaction is performed with anticipated resignation to the ensuing product mixture with subsequent efforts directed toward separation of the congeners.[4] One approach to this problem, however, is externally altering (or ideally overpowering) the diastereofacial selectivities of the reactants. The use of enolates

† This paper is dedicated to Professor Frederick D. Greene in appreciation of his 27 years of service as Editor of *The Journal of Organic Chemistry*.

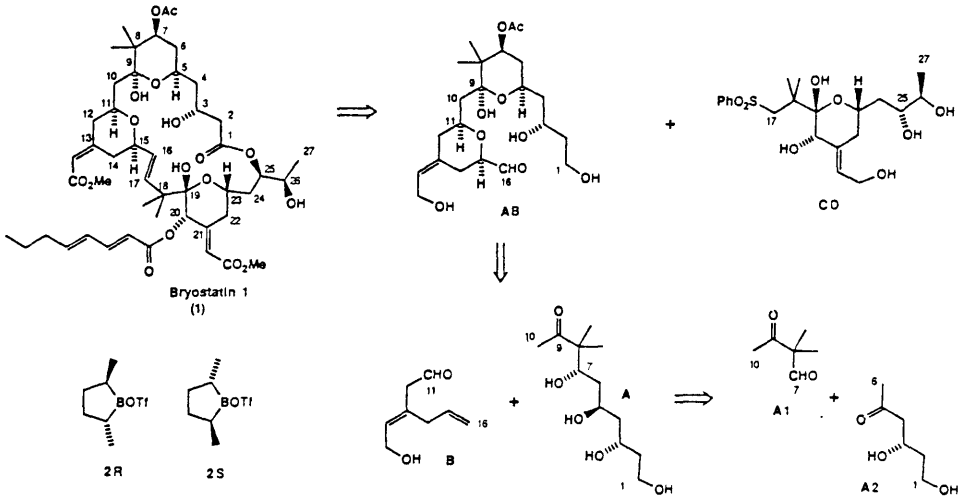
(1) Pettit, G. R.; Day, J. F.; Hartwell, J. L.; Wood, H. B. *Nature (London)* 1970, *227*, 962.

(2) (a) Pettit, G. T.; Herald, C. L.; Doubec, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* 1982, *104*, 6846. (b) Pettit, G. R.; Kamano, Y.; Herald, C. L. *J. Org. Chem.* 1987, *52*, 2854 and references cited therein.

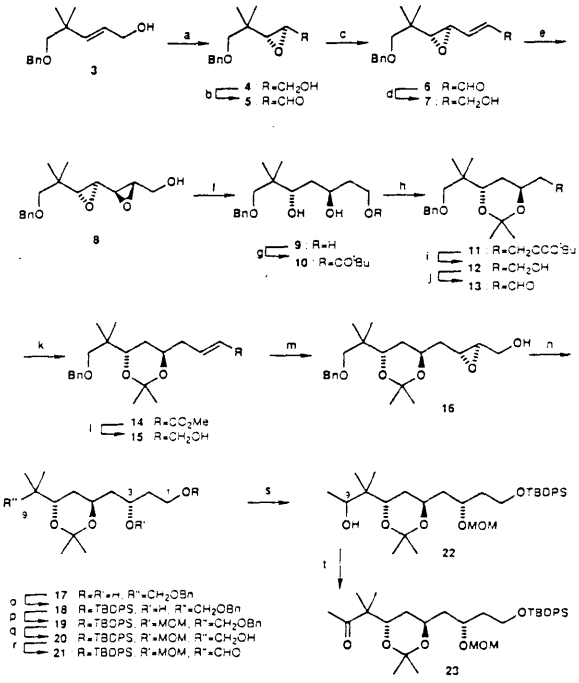
(3) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* 1985, *24*, 1. (b) Masamune, S. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH Verlagsgesellschaft mbH: Weinheim, 1987; pp 49–71. As discussed in these references, the process of fragment assembly should be distinguished from one whereby stereogenic centers are created on a chiral substrate by a homochiral reagent or catalyst, as has been executed on numerous occasions in recent years.

(4) For instance, see: (a) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* 1986, *27*, 4741. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* 1988, *110*, 2506.

Scheme I

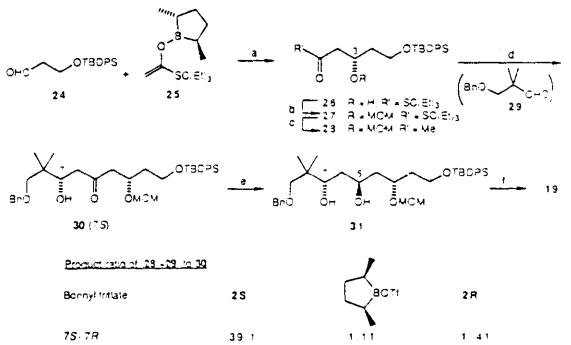


Scheme II[a]



[a] (a) (−)-DET, $Ti(iPrO)_4$, TBHP, CH_2Cl_2 (85%); (b) $(COCl)_2$, DMSO, CH_2Cl_2; (c) $Ph_3PCHCHO$, benzene; (d) $NaBH_4$, MeOH (61%, three steps); (e) (+)-DET, $Ti(iPrO)_4$, TBHP, CH_2Cl_2 (80%); (f) Red-Al, THF; (g) tBuCOCl, pyridine, CH_2Cl_2 (55%, two steps); (h) $(CH_3)_2C(OMe)_2$, PPTS (94%); (i) DIBAL, Et_2O (95%); (j) $(COCl)_2$, DMSO, CH_2Cl_2; (k) $(EtO)_2P(O)CH_2CO_2Me$, NaH, toluene (88%, two steps); (l) DIBAL, Et_2O (87%); (m) (−)-DET, $Ti(iPrO)_4$, TBHP, CH_2Cl_2 (80%); (n) Red-Al, THF; (o) TBDPS-Cl, imidazole, DMF (86%, two steps); (p) MOMBr, iPr_2EtN (85%); (q) W-2 RaNi, EtOH (88%); (r) $(COCl)_2$, DMSO, CH_2Cl_2; (s) MeLi, THF; (t) $(COCl)_2$, DMSO, CH_2Cl_1 (93%, three steps).

Scheme III[a]



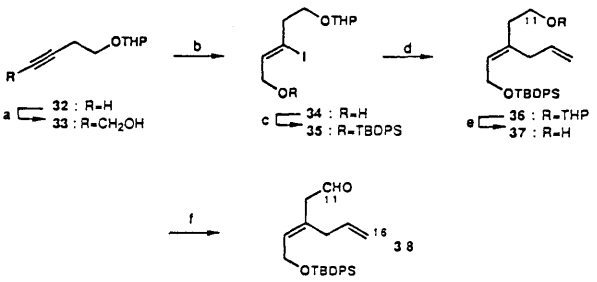
[a] (a) Pentane (79%, 89% ee); (b) $(MeO)_2CH_2$, P_2O_5, $CHCl_3$ (91%); (c) $LiCuMe_2$, Et_2O (91%); (d) (i) iPr_2EtN, **2R**, pentane–Et_2O; (ii) **29** (87%); (e) $Me_4NBH(OAc)_3$, AcOH–MeCN (86%); (f) $(CH_3)_2C(OMe)_2$, PPTS, CH_2Cl_2 (98%).

derived from chiral ketones and a chiral boron reagent, e.g. (*R,R*)- or (*S,S*)-2,5-*trans*-dimethylborolanyl trifluoromethanesulfonate (**2R** and **2S**),[5] instead of an achiral boron reagent such as diethylboryl trifluoromethanesulfonate[6] exemplifies this approach. The stereochemical course of the coupling reaction may be analyzed in terms of the diastereofacial selectivity of (i) the chiral ligands attached to boron and (ii) the chiral fragment or fragments. The external chiral reagent is thus designed and selected to serve as the major controlling factor, directing the stereochemical outcome predictably. This paper highlights our initial efforts directed toward solving this important problem.[7]

Synthesis of Fragment A [C(1)–C(10)]. Comparison of our two syntheses of the A fragment, outlined in Schemes II and III, demonstrates the relative simplicity of Scheme III, which adopts a convergent, fragment-coupling approach. Our original route (Scheme II) utilizes Red-Al (Aldrich) ring opening of epoxy alcohols to provide 1,3-diols, a method available at the onset of this project.[8] This reaction sequence proceeds uneventfully and does not require much explanation. The epoxidation of allylic alcohol 3[9] affords 4 (85%, 92% ee), which, after oxidation

(5) Masamune, S.; Sato, T.; Kim, B.-M.; Wollmann, T. A. *J. Am. Chem. Soc.* 1986, *108*, 8279.
(6) Mukaiyama, T.; Inoue, T. *Chem. Lett.* 1976, 559.
(7) For articles related to this subject, see: (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* 1983, *105*, 6968. (b) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* 1987, *28*, 1229.
(8) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* 1982, *47*, 1373.
(9) Allylic alcohol 3 was prepared from aldehyde 29 in two steps (see ref 15).

Scheme IV[a]



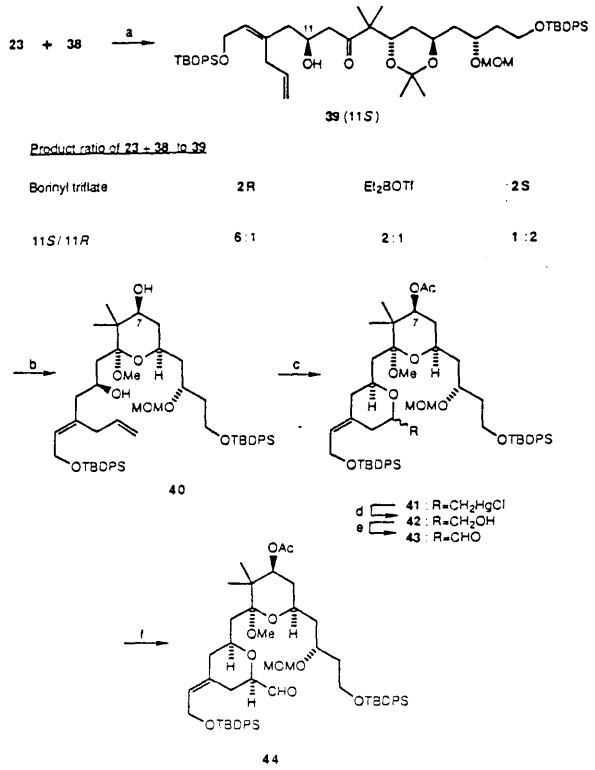
[a] (a) BuLi, HCOH(g), THF (89%); (b) Red-Al, THF, then I_2 (90%); (c) TBDPS-Cl, iPr_2EtN, imidazole, CH_2Cl_2 (95%); (d) allylMgBr, CuI, Et_2O (77%); (e) EtOH, PPTS (92%); (f) $(Py)_2CrO_3$, CH_2Cl_2.

to aldehyde **5**, formylolefination, and reduction, is converted to allylic alcohol **7** (61%, three steps). The following epoxidation affords bisepoxide **8** (80%, >98% de). Directed double ring opening by treatment with Red-Al followed by hydroxyl group differentiation leads to alcohol **12** (50%, four steps). An analogous sequence of Swern oxidation, Horner–Emmons olefination, reduction, epoxidation, and ring opening yields diol **17** (65%, five steps). Subsequent protection of the C(1) and C(3) alcohols,[10] and deprotection of the C(9) alcohol, affords **20** (64%, three steps), which is subsequently converted to fully protected fragment A, methyl ketone **23** (71%, three steps).

Although each step of Scheme II proceeds smoothly to afford a product of *secured* stereochemical assignment (which served the purpose of confirming the stereochemistry of **19** obtained through the route shown in Scheme III), the sequence is obviously too lengthy. This drawback has been remedied by the application of our recent stereoselective aldol methodology utilizing external chiral reagent control. This convergent synthesis, with less than half the steps, begins with aldehyde **24**,[11] which is converted to thioester **26** (79%, 89% ee) with our homochiral acetate equivalent: boron enolate reagent **25**.[5] Although treatment of **26** with methoxymethyl bromide under standard conditions affords only low yields of MOM ether **27** (40–50%),[12] the less utilized procedure with dimethoxymethane and P_2O_5 completes this task satisfactorily (91%).[13] Conversion to methyl ketone **28** ensues upon treatment with lithium dimethylcuprate (94%).[14]

In the subsequent coupling reaction, external chiral reagent **2S** (Scheme I), selective for the desired stereochemistry, is utilized. Thus the boron enolate derived from **2S** and **28** is condensed with aldehyde **29**,[15] providing **30** (87%) as an inseparable mixture of diastereomers. Directed reduction of this mixture with the Saksena–Evans reagent $[Me_4NBH(OAc)_3]$[16] leads to **31** (86%) as a 3.9:1 mixture of separable diastereomers. Consistent with our intuition that this product ratio reflects the ratio obtained

Scheme V[a]



[a] (a) **2R**, iPr_2EtN, pentane (86%); (b) MeOH, PPTS (84%); (c) (i) $Hg(OAc)_2$, THF–MeOH, then KCl; (ii) AcCl, pyridine, CH_2Cl_2 (80–90%, two steps); (d) $NaBH_4$, O_2, DMF (70–80%); (e) $(COCl)_2$, DMSO, CH_2Cl_2 (85%); (f) Al_2O_3 (3% H_2O), CH_2Cl_2.

in the aldol reaction is that the use of an achiral reagent (*meso*-2,5-dimethylboranyl triflate)[17] and subsequent reduction affords **31** as a 1:1.1 ratio of diastereomers. Similarly, the use of **2R**, selective for the undesired diastereomer, leads to a 1:4.1 ratio. In these coupling reactions, ketone **28** happens to behave like an achiral methyl ketone and the 30(7*S*)/30(7*R*) ratios in the matched and mismatched reactions simply reflect the diastereofacial selectivity of the chiral reagent **2R** or **2S** (apparent single asymmetric synthesis). The synthesis of **19** was completed by acetonide formation on diol **31** (98%), and the C(7) and C(5) stereochemistry was confirmed by comparison with compound **19**, prepared via the route described earlier in Scheme II.

Synthesis of Fragment B [C(11)–C(16)]. The B fragment is synthesized in a straightforward manner as outlined in Scheme IV. Thus, one-carbon extension on THP ether **32**[18] affords alcohol **33** (89%). Application of Corey's trisubstituted olefin synthesis provides **36** (74%, three steps) via iodides **34**[19,20] and **35**. Subsequent C(11) alcohol deprotection followed by Collins oxidation affords aldehyde **38**, fully protected fragment B, which is used without purification.

Synthesis of Fragment AB [C(1)–C(16)]. The completion of the AB portion of bryostatin 1, outlined in

(10) Hanessian, S.; Lavallee, P. *Can. J. Chem.* 1975, *53*, 2975.
(11) Aldehyde **24** was prepared from *cis*-3-hexen-1-ol in two steps, and its use has been described on one previous occasion: Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* 1988, *110*, 3979.
(12) (a) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* 1972, *94*, 782. (b) Stork, G.; Takahashi, T. *Ibid.* 1977, *99*, 1275.
(13) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* 1976, 276.
(14) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* 1985, *107*, 4549.
(15) The preparation of aldehyde **29** from 2,2-dimethyl-1,3-propanediol in two or three steps has been described several times; for example, see: Yeh, C.-L.; Dawson, M.; Hemler, M. E.; Lands, W. E. M. *Tetrahedron Lett.* 1977, 4257.
(16) (a) Saksena, A. K.; Mangiaraeina, P. *Tetrahedron Lett.* 1983, *24*, 273. (b) Evans, D. A.; Chapman, K. T. ibid. 1986, *27*, 5939. (c) Evans, D. A.; Dimare, M. *J. Am. Chem. Soc.* 1986, *108*, 2476.
(17) Kim, B.-M. Ph.D. Thesis, MIT, 1987.
(18) The preparation of THP ether **32** has been described previously, for example, see: Jones, E. R. K.; Shen, T. J.; Whiting, M. C. *J. Chem. Soc., Chem. Commun.* 1950, 230.
(19) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* 1967, *89*, 4245.
(20) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* 1982, *47*, 4595–4597.

Scheme V, begins with the crucial step of coupling fragments A and B. Reaction of **38** with the enolate derived from **23** and **2R** provides ketol **39** as a mixture of inseparable diastereomers. The first pyran cyclization, which ensues upon deacetonization in methanol, affords methyl acetal **40** (84%) as a 6:1 ratio of separable diastereomers. Again, consistent with our notion that this product ratio reflects the ratio obtained in the aldol condensation are the results that (i) the use of an achiral reagent (diethylboryl triflate)[6] and subsequent pyran formation affords **40** as a 2:1 ratio of diastereomers and (ii) similarly the use of **2S** leads to a 1:2 ratio.[21] Note that the desired stereochemistry is obtained by the complimentary selectivities of **38** and **2R** (a matched case).[3a] Furthermore, the above ratios of diastereomers observed for both the matched and mismatched pairs are in accord with the approximate multiplicativity rules of double asymmetric synthesis.[3a]

The synthesis of the AB fragment was completed by a second pyran formation on methyl acetal **40**. This stereorandom cyclization is triggered by treatment with $Hg(OAc)_2$ to afford an organomercurial intermediate, which, after acetylation of the C(7) alcohol, yields **41** (85%).[22] Oxidative demercuration leads to alcohol **42** (75%), and Swern oxidation affords aldehyde **43** (85%) as a 1:1 equatorial–axial mixture. Subsequent equilibration to a 9:1 equatorial–axial mixture of aldehydes is effected with Al_2O_3, thereby concluding the synthesis of **44**, the AB fragment.[23]

Experimental Section

Boiling points and melting points are uncorrected. Reactions were run in oven-dried glassware under Ar or N_2. All homogeneous liquid reagents other than chlorodiphenyl*tert*-butylsilane were distilled under N_2 before use. Amines, CH_2Cl_2, DMF, DMSO, MeCN, pyridine, and benzene were distilled from CaH_2 under N_2. Ether and THF were likewise distilled from $LiAlH_4$, $CHCl_3$ from P_2O_5, and AcOH from CrO_3. Column chromatography was performed with 230–400 mesh silical gel (Merck), and preparative TLC was performed with UNIPLATE thin-layer chromatography plates (Analtech). ^1H NMR spectra were recorded at 250 MHz on a Bruker WM 250 spectrometer or at 300 MHz on a Varian XL-300 spectrometer (as indicated), and ^{13}C NMR spectra were recorded at 75.4 MHz on a Varian XL-300. IR spectra were recorded on a Perkin-Elmer 283B spectrometer. Optical rotations were recorded at ambient temperature on an Autopol III polarimeter. Mass spectra were obtained by using a Finnigan MAT 8200 spectrometer.

Experimental Procedures for Scheme II: Fragment A via Sharpless Epoxidation. Allylic Alcohol 3 (via aldehyde 29). A magnetically stirred solution of 2,2-dimethyl-1,3-propanediol (85 g, 0.81 mol), benzaldehyde (73 g, 0.69 mol), and *p*-TsOH (10 mg) dissolved in benzene (0.2 L) was heated at reflux temperature for 14 h. After 12 mL of water was collected by means of a Dean–Stark apparatus, the solution was cooled to 25 °C and extracted with 10% NaOH(aq) and then water. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by Kugelrohr distillation (123–127 °C, 4.0 mm) to yield 124 g (91%) of the benzylidine acetal as an oil, which crystallized upon standing to a white solid: mp 29–30 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 1.28 (s, 3 H), 3.58 (d, J = 11.3 Hz, 1 H), 3.72 (d, J = 11.3 Hz, 1 H), 4.49 (s, 1 H), 7.33 (m, 5 H); MS (m/z) $[M]^+$ 191, 107, 105.

To a magnetically stirred solution of this benzylidene acetal (140 g, 0.72 mol) dissolved in THF (0.8 L) was added dropwise BH_3·THF (1 M, 800 mL, 0.8 mol). The colorless solution was heated at reflux temperature for 72 h, after which it was allowed to cool to room temperature before being quenched by the dropwise addition of methanol (0.5 L). The solution was concentrated in vacuo, and the residual oil was dissolved in ether. The ethereal solution was extracted with 0.1 N HCl and brine. The aqueous extracts were back-extracted with ether, and the combined organic phase was then dried over $MgSO_4$. Upon filtration and concentration in vacuo, the residual oil was purified by fractional distillation (123–126 °C, 2.5 mm) to give 132 g (94%) of the alcohol: IR (neat) 3450, 3020, 2980, 2870, 1075 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (s, 6 H), 2.87 (s, 1 H), 3.31 (s, 2 H), 3.43 (s, 2 H), 4.50 (s, 2 H), 7.32 (m, 5 H); HRMS $[M]^+$ calcd 194.1307, found 194.1306.

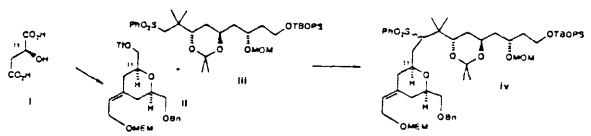
A solution of this alcohol (21 g, 108 mmol) dissolved in CH_2Cl_2 (50 mL) was added dropwise to a rapidly stirred solution of PCC (34 g, 158 mmol) dissolved in CH_2Cl_2 (0.2 L). The initially bright orange solution immediately turned black. Five reactions were set up simultaneously in this fashion and were allowed to proceed at 25 °C. An additional 4.5 g of PCC was added to each reaction after 8 h to ensure complete reaction. After an additional 3 h each reaction was diluted with ether (150 mL). The organic phase was decanted, and the remaining gummy black residue was washed with ether (3 × 75 mL). The combined organic extract was filtered through a column of florisil and concentrated in vacuo to afford 101 g of crude material. Purification by Kugelrohr distillation (78–83 °C, 2.5mm) gave 86.2 g (82%) of **29**: IR (neat) 2980, 1730, 1450, 1100, 890, 730, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.06 (s, 6 H), 3.41 (s, 2 H), 4.46 (s, 2 H), 7.28 (m, 5 H), 9.52 (s, 1 H).

Triethyl phosphonoacetate (132 mL, 664 mmol) was added dropwise to a magnetically stirred 0 °C slurry of sodium hydride (80% dispersion in mineral oil, 19.6 g, 610 mmol) suspended in toluene (1.2 L). To the resulting clear solution was added a solution of aldehyde **29** (86 g, 447 mmol) dissolved in THF (0.1 L). The reaction was stirred at 0 °C for 1 h, whereupon it was allowed to warm to ambient temperature and stir for an additional 6 h. The reaction was quenched by addition of saturated NaCl(aq), and the organic phase was separated. The aqueous phase was extracted with ether, and the combined organic phases were concentrated in vacuo. Flash SiO_2 chromatography (10:1 hexane/ethyl acetate) on the residual yellow oil gave 104 g (89%) of the unsaturated methyl ester: IR (neat) 2960, 2860, 1715, 1645, 1450, 1360, 1270, 1170, 1090, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 6 H), 1.27 (t, J = 7.1 Hz, 3 H), 3.24 (s, 2 H), 4.17 (q, J = 7.1 Hz, 2 H), 4.49 (s, 2 H), 5.80 (d, J = 16 Hz, 1 H), 7.01 (d, J = 16 Hz, 1 H), 7.29 (m, 5 H); MS (m/z) $[M]^+$ 262, 176, 141, 91.

To a solution of this unsaturated methyl ester (104 g, 396 mmol) dissolved in ether (1.5 L) at −78 °C was added dropwise DIBAL (25% solution in toluene, 672 mL, 1 mol). The reaction mixture was stirred overnight at 25 °C and subsequently quenched by the addition of methanol (0.7 L). The precipitated salts were dissolved with 1.0 N HCl(aq) (0.3 L), and the organic phase was separated. The aqueous phase was extracted with ether and then ethyl acetate. The combined oranic extracts were concentrated in vacuo to afford 84 g of a light yellow oil readily purified by Kugelrohr distillation (124–132 °C, 0.2 mm) to give 69 g (79%) of **3**: IR (neat) 3380, 3010, 2960, 2860, 1450, 1355, 1080, 1020, 965, 725, 675 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (s, 3 H), 1.60 (br s, 1 H), 3.21 (s, 2 H), 4.08 (d, J = 5.3 Hz, 2 H), 4.48 (s, 2 H), 5.60 (dt, J = 16, 5.3 Hz, 1 H), 5.75 (d, J = 16 Hz, 1 H), 7.29 (m, 5 H); HRMS $[M]^+$ calcd 220.1463, found 220.1463.

Epoxy Alcohol 4. To a mechanically stirred mixture of CH_2Cl_2 (1.5 L) and activated powdered 4-Å molecular sieves (40 g) was added titanium(IV) isopropoxide (30 mL, 100 mmol). After the mixture was cooled to −40 °C, (−)-diethyl D-tartrate (23 mL, 134

(21) Additional confirmation of the C(11) stereochemistry has been made. In brief, the route outlined below starting from i led to iv with the unambiguously assigned stereochemistry at C(11) (the same as that of i). Both **44** and iv were transformed to an identical derivative. The synthetic route from i to iv is superceded by that described in the text and is therefore not elaborated on.



(22) Whitesides, G. M.; Hill, C. L. *J. Am. Chem. Soc.* 1974, *96*, 870.

(23) A preliminary account of this work was presented at the Seventh IUPAC Conference on Organic Synthesis held in Nancy, France (July 4–7, 1988): Masamune, S. *Pure Appl. Chem.* 1988, *60*, 1587.

mmol) was added, and the resultant mixture was stirred for 15 min. A solution of **3** (112 g, 510 mmol) in CH_2Cl_2 (0.1 L) was then added, and stirring was continued for 30 min prior to the addition of anhydrous *tert*-butyl hydroperoxide (4.0 M in toluene, 330 mL, 1.32 mol). The reaction mixture was allowed to warm to 0 °C over 8 h, whereupon it was poured into a 6-L Erlenmeyer flask containing a 0 °C mixture of ether (2 L), ferrous sulfate (165 g, 590 mmol), and tartaric acid (66 g, 440 mmol) dissolved in water (670 mL). Upon vigorous mixing the aqueous layer turned dark brown. The mixture was stirred at 25 °C for 1 h, after which the layers were separated. The aqueous layer was extracted with ether and ethyl acetate. The combined organic extract was concentrated in vacuo to afford a yellow oil, which was dissolved in ether (1.1 L) and added with vigorous mechanical stirring to a 0 °C solution of NaOH (s) (17 g, 425 mmol) in saturated NaCl(aq) (0.4 L). After 2.5 h, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extract was concentrated in vacuo, and the residual oil was purified by SiO_2 flash chromatography (5:1 hexane/ethyl acetate) to give 102 g (85%) of **4**: $[\alpha]^{24}_D$ +8.38° (*c* 2.50, $CHCl_3$); IR (neat) 3425, 2960, 2860, 1450, 1360, 1160, 1040, 890, 728, 688 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (s, 6 H), 1.70 (br s, 1 H), 2.92 (d, J = 2.3 Hz, 1 H), 3.09 (m, 1 H), 3.22 (A of AB d, J = 8.7 Hz, 1 H), 3.27 (B of AB d, J = 8.7 Hz, 1 H), 3.55 (dd, J = 12, 6.3 Hz, 1 H), 3.85 (dd, J = 12, 2.2 Hz, 1 H), 4.51 (s, 2 H), 7.32 (m, 5 H); MS (*m/z*) [M − H_2O]$^+$ 218, 187, 107, 91.

Aldehyde 5. To a mechanically stirred solution of oxalyl chloride (42 mL, 475 mmol) in CH_2Cl_2 (1.2 L) at −78 °C was added dropwise, over 30 min, DMSO (67 mL, 951 mmol). Upon complete addition, **4** (56.2 g, 238 mmol) dissolved in CH_2Cl_2 (150 mL) was added dropwise over 40 min. The initially clear solution became white and cloudy after stirring for 1.5 h. Triethylamine (170 mL, 1.19 mol) was then added dropwise while the reaction temperature was maintained at −78 °C. Upon complete addition, the reaction mixture was warmed slowly to −10 °C over 2.5 h and then quenched by addition of water (100 mL). The organic layer was separated and washed several times with water and then with saturated NaCl(aq). The combined aqueous washes were back-extracted with CH_2Cl_2. The organic extracts were combined and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was filtered through a plug of SiO_2 (10:1 hexane/ethyl acetate) to give **5** as a yellow oil (57 g), which was used in the next step without further purification: IR (neat) 3422, 2960, 2860, 1723, 1450, 1360, 1172, 1090, 845, 725, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (s, 3 H), 0.88 (s, 3 H), 3.21 (m, 4 H), 4.44 (s, 2 H), 7.27 (m, 5 H), 8.96 (d, J = 6.1 Hz, 1 H).

Unsaturated Aldehyde 6. A solution of crude **5** (57 g) in THF (100 mL) was added with vigorous overhead mechanical stirring to a 0 °C slurry of (formylmethylene) triphenylphosphorane (91 g, 300 mmol) in benzene (1.6 L). The resultant slurry was stirred for 12 h at 0 °C, whereupon the suspended solids were filtered. The filtrate was concentrated in vacuo to a yellow oil containing white solids (triphenylphosphine oxide). The oil was triturated with 2:1 hexane/ethyl acetate (8 × 50 mL), and the extracts were combined and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (12:1 hexane/ethyl acetate) to give 34.2 g (55%, two steps) of **6**: IR (neat) 2960, 2860, 1725, 1688, 1450, 1360, 1175, 1085, 850, 728, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 0.94 (s, 3 H), 2.86 (d, J = 1.9 Hz, 1 H), 3.16 (A of AB, J = 8.8 Hz, 1 H), 3.20 (B of AB, J = 8.8 Hz, 1 H), 3.45 (dd, J = 6.7, 2.0 Hz, 1 H), 4.43 (s, 2 H), 6.27 (dd, J = 16, 6.7 Hz, 1 H), 6.45 (dd, J = 16, 6.0 Hz, 1 H), 7.27 (m, 5 H), 9.48 (d, J = 7.4 Hz, *E*-C*H*O).

Allylic Alcohol 7. To a magnetically stirred solution of **6** (34.2 g, 131 mmol) in methanol (0.6 L) at −50 °C was added portionwise sodium borohydride (7.9 g, 208 mmol). The resultant white suspension was stirred at −20 °C for 6 h, whereupon the reaction was quenched by dropwise addition of water (15 mL). The methanol was removed in vacuo, and the residual oil was dissolved in ether (300 mL). The organic solution was washed with water and saturated NaCl(aq) and dried over $MgSO_4$. After filtration and concentration in vacuo, the crude oil was purified by SiO_2 flash chromatography (4:1 hexane/ethyl acetate) to afford 30.5 g (93%) of **7**: $[\alpha]^{24}_D$ +0.90° (*c* 1.7, $CHCl_3$); IR (neat) 3410, 2960, 2860, 1450, 1360, 1201, 1085, 1015, 960, 880, 728, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 0.93 (s, 3 H), 1.30 (br s, 1 H), 2.60 (d, J = 2.3 Hz, 1 H), 3.26 (m, 3 H), 4.18 (t, J = 4.5 Hz, 2 H), 4.49 (s, 3 H), 5.48 (dd, J = 15, 7.6 Hz, 1 H), 6.95 (dt, J = 16, 5.2 Hz, 1 H), 7.32 (m, 5 H); MS (*m/z*) [M]$^+$ 262, 245, 107, 91.

Bisepoxide 8. To a mechanically stirred suspension of powdered 4-Å molecular sieves (25 g) in CH_2Cl_2 (0.8 L) at −40 °C was added titanium(IV) isopropoxide (14.5 mL, 49 mmol) followed by addition of (+)-diethyl L-tartrate (11 mL, 64 mmol). After the mixture was stirred 15 min, a solution of **7** (64 g, 244 mmol) in CH_2Cl_2 (80 mL) was added, and stirring was continued for 30 min prior to the addition of anhydrous *tert*-butyl hydroperoxide (4.0 M solution in toluene, 120 mL, 480 mmol). The reaction mixture was warmed to 0 °C over 12 h and subsequently poured into a 3-L Erlenmeyer flask containing ether (1 L) and saturated Na_2SO_4(aq) (130 mL). The resultant solution was stirred vigorously for 2 h, whereupon the solids were filtered and triturated with hot ethyl acetate (2 × 350 mL). The combined organic phases were concentrated in vacuo, and the residual oil was dissolved in ether (1.5 L). The ether solution was then added with rapid mechanical stirring to a 0 °C solution of NaOH(s) (20 g, 0.5 mol) in saturated NaCl(aq) (0.6 L). After 2 h the aqueous layer was separated and extracted with ether and then ethyl acetate. The combined organic phases were concentrated in vacuo, and the residual oil was purified by SiO_2 flash chromatography (4:1 hexane/ethyl acetate) to give 54.5 g (80%) of **8**: IR (neat) 3445, 2960, 2860, 1450, 1360, 1090, 1220, 890, 728, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 0.89 (s, 3 H), 1.94 (t, J = 5.6 Hz, 1 H), 2.86 (d, J = 2.3 Hz, 1 H), 2.96 (m, 1 H), 3.04 (d, J = 3.6 Hz, 2 H), 3.28 (A of AB d, J = 8.8 Hz, 1 H), 3.32 (B of AB d, J = 8.8 Hz, 1 H), 3.60 (m, 1 H), 3.85 (dd, J = 11, 3.6 Hz, 1 H), 4.49 (s, 2 H), 7.30 (m, 5 H).

Triol 9. To a −40 °C solution of **8** (25.5 g, 92 mmol) in THF (750 mL) was added Red-Al (3.5 M solution in toluene, 130 mL, 455 mmol) dropwise over 1 h. The reaction was allowed to warm to ambient temperature and stirred for 2 days. The reaction was quenched by slow cannulation of the reaction mixture into a saturated solution of Rochelle's salt (aq) (1 L) with vigorous mixing. Ether (500 mL) was added upon complete cannulation, and after the mixture was stirred for an additional 30 min, the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried over $MgSO_4$. After filtration, the solvents were removed in vacuo to afford 25 g of the crude **9** as a viscous oil, which was used in the next step without further purification. A small sample was purified by SiO_2 chromatography (9:1 $CHCl_3$/MeOH) for analytical purposes: IR ($CHCl_3$) 3485, 2880, 1465, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 0.85 (s, 3 H), 1.50 (m, 2 H), 1.75 (m, 1 H), 2.68 (br s, 3-O*H*), 3.30 (A of AB d, J = 7.6 Hz, 1 H), 3.37 (B of AB d, J = 7.6 Hz, 1 H), 3.82 (m, 3 H), 4.12 (m, 1 H), 4.47 (AB apparent singlet, 2 H), 7.27 (m, 5 H); MS (*m/z*) [M]$^+$ 282, 174, 108, 101, 91.

Pivalate Ester 10. To a magnetically stirred 0 °C solution of crude **9** (25 g) in CH_2Cl_2 (650 mL) was added pyridine (14.2 mL, 177 mmol) followed by dropwise addition of pivaloyl chloride (21.7 mL, 177 mmol). After being stirred for 4 h, the reaction mixture was diluted with ether (0.8 L) and subsequently washed with saturated $CuSO_4$(aq) (3 × 100 mL). The combined aqueous washes were back-extracted with ethyl acetate (3 × 100 mL). The combined organic extract was then dried over $MgSO_4$, filtered, and concentrated in vacuo to a light yellow oil. Hexane (100 mL) was added, and the solution was cooled to 0 °C, whereupon crystallization occurred. The crystals were collected by suction filtration and dried in vacuo to give 18.3 g (55%, two steps) of **10**: mp 77 °C; $[\alpha]^{24}_D$ −8.9° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3480, 2960, 2870, 1720, 1285, 1160, 1080 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (s, 3 H), 0.92 (s, 3 H), 1.20 (s, 9 H), 1.50 (m, 2 H), 1.82 (m, 2 H), 2.90 (m, 1 H), 3.35 (dd, J = 16, 8.8 Hz, 2 H), 3.60 (m, 1 H), 3.80 (m, 1 H), 3.90 (m, 1 H), 4.25 (m, 1 H), 4.33 (m, 1 H), 4.98 (A of AB d, J = 12 Hz, 1 H), 5.00 (B of AB d, J = 12 Hz, 1 H), 7.35 (m, 5 H); HRMS [M]$^+$ calcd 366.2406, found 366.2405.

Acetonide 11. To a magnetically stirred 24 °C solution of **10** (18.3g, 50 mmol) in CH_2Cl_2 (300 mL) was added 2,2-dimethoxypropane (55 mL, 500 mmol) and *p*-TsOH (100 mg, 0.64 mmol). The reaction was complete after 2 h (as indicated by TLC) and subsequently quenched by washing with saturated $NaHCO_3$(aq) followed by saturated NaCl(aq). The organic phase was then dried

over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (4:1 hexane/ethyl acetate) to yield 19.2 g (94%) of 11: $[\alpha]^{24}_D$ −8.48° (*c* 4.00, $CHCl_3$); IR (neat) 2960, 2860, 1730, 1475, 1450, 1380, 1280, 1220, 1160, 1090, 920, 880, 725, 687 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 0.90 (s, 3 H), 1.19 (s, 9 H), 1.27 (s, 3 H), 1.29 (s, 3 H), 1.40 (m, 1 H), 1.75 (m, 3 H), 3.16 (d, *J* = 8.6 Hz, 1 H), 3.30 (d, *J* = 8.6 Hz, 1 H), 3.81 (dd, *J* = 9.9, 6.3 Hz, 2 H), 4.13 (t, *J* = 6.4 Hz, 2 H), 4.49 (A of AB d, *J* = 13 Hz, 1 H), 4.45 (B of AB d, *J* = 13 Hz, 1 H), 7.32 (m, 5 H); MS (*m/z*) $[M - C_4H_9]^+$ 349, 265, 185, 91.

Alcohol 12. To a solution of 11 (19.2g, 42 mmol) in ether (0.6L) at −78 °C was added DIBAL (1 M solution in hexane, 95 mL, 95 mmol) dropwise. After 1 h, the reaction was quenched by the dropwise addition of methanol (150 mL) and warmed to 25 °C over 1 h, whereupon white salts precipitated. The salts were filtered through a Buchner funnel and washed with a 1:1:1 mixture of hexane/ethyl acetate/methanol. The combined organic phases were concentrated in vacuo to afford a colorless oil, which was purified by SiO_2 flash chromatography (8:1 hexane/ethyl acetate) to give 14.4 g (95%) of 12: $[\alpha]^{24}_D$ −28.44° (*c* 2.7, $CHCl_3$); IR (neat) 3425, 2960, 2860, 1450, 1370, 1215, 1090, 960, 725, 680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 0.90 (s, 3 H), 1.30 (s, 3 H), 1.33 (s, 3 H), 1.39 (m, 1 H), 1.74 (m, 3 H), 2.59 (t, *J* = 4.9 Hz, 1 H), 3.16 (d, *J* = 8.6 Hz, 1 H), 3.29 (d, *J* = 8.6 Hz, 1 H), 3.80 (m, 3 H), 3.95 (m, 1 H), 4.46 (A of AB d, *J* = 12 Hz, 1 H), 4.50 (B of AB d, *J* = 12 Hz, 1 H), 7.33 (m, 5 H); MS (*m/z*) $[M - CH_3]^+$ 307, 266, 159, 92, 91.

Aldehyde 13. Dimethyl sulfoxide (9 mL, 129 mmol) was added dropwise to a solution of oxalyl chloride (5.50 mL, 64.5 mmol) in CH_2Cl_2 (250 mL) at −78 °C. Upon complete addition, a solution of 12 (10.4g, 32.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise, and stirring was continued at −78 °C. After 1 h, triethylamine (23 mL, 161 mmol) was added, and the reaction mixture was allowed to warm to 0 °C over 2 h. The reaction solution was then poured into water (50 mL), and the layers were separated. The organic layer was washed with additional water and saturated NaCl(aq). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield crude 13. Partial purification was accomplished by SiO_2 flash chromatography (6:1 hexane/ethyl acetate) to give 10.5 g of a yellow oil, which was used in the next step without further purification: IR ($CHCl_3$) 2880, 1735, 1520, 1370, 1250, 1170, 1090, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 3 H), 0.83 (s, 3 H), 1.22 (s, 3 H), 1.25 (s, 3 H), 1.36 (ddd, *J* = 12, 9.7, 6.2 Hz, 1 H), 1.82 (ddd, *J* = 12, 9.6, 5.8 Hz, 1 H), 2.39 (ddd, *J* = 16, 4.2, 2.5 Hz, 1 H), 2.52 (ddd, *J* = 13, 11, 2.5 Hz, 1 H), 3.09 (d, *J* = 9.0 Hz, 1 H), 3.23 (d, *J* = 8.9 Hz, 1 H), 3.76 (dd, *J* = 9.6, 6.2 Hz, 1 H), 4.18 (m, 1 H), 4.35 (A of AB d, *J* = 12 Hz, 1 H), 4.41 (B of AB d, *J* = 12 Hz, 1 H), 7.26 (m, 5 H), 9.67 (t, *J* = 3.6 Hz, 1 H).

Unsaturated Methyl Ester 14. Triethyl phosphonoacetate (9 mL, 49 mmol) was added dropwise to a 0 °C slurry of sodium hydride (80% dispersion in mineral oil, 1.2 g, 45.9 mmol) suspended in toluene (250 mL). After the mixture was stirred for 1 h, crude 13 (10.5 g) dissolved in THF (50 mL) was added dropwise over 30 min. Stirring was continued at 0 °C for 10 h, whereupon the reaction was quenched with water. The organic layer was separated and washed with additional water and saturated NaCl(aq). The combined aqueous washes were back-extracted with ether, and the combined organic extracts were concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (20:1 hexane/ethyl acetate) to yield 10.9 g (88%, two steps) of 14: IR (neat) 2965, 2860, 1718, 1648, 1450, 1375, 1215, 1085, 960, 730, 680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.89 (s, 3 H), 1.29 (t, *J* = 6.8 Hz, 3 H), 1.30 (s, 6 H), 1.35 (m, 1 H), 1.80 (m, 3 H), 2.37 (m, 2 H), 3.15 (d, *J* = 8.6 Hz, 1 H), 3.29 (d, 8.5 Hz, 1 H), 3.83 (m, 2 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 4.45 (A of AB d, *J* = 12 Hz, 1 H), 4.49 (B of AB d, *J* = 12 Hz, 1 H), 5.88 (d, *J* = 16 Hz, 1 H), 6.93 (dt, *J* = 16, 6.9 Hz, 1 H), 7.33 (m, 5 H); HRMS $[M - CH_3]^+$ calcd 375.2171, found 375.2169.

Allylic Alcohol 15. To a solution of 14 (10.1 g, 26 mmol) in ether (0.6 L) at −78 °C was added DIBAL (1 M solution in hexane, 64 mL, 64 mmol). The reaction was quenched after 2 h at −78 °C by dropwise addition of water (20 mL). The precipitated salts were filtered and washed several times with ethyl acetate. All filtrates were combined and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (8:1 hexane/ethyl acetate) to afford 7.8 g (87%) of 15: $[\alpha]^{24}_D$ −30.11° (*c* 0.445, $CHCl_3$): IR (neat) 3380, 2940, 2860, 1450, 1370, 1220, 1080, 995, 720, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.89 (s, 3 H), 1.30 (s, 6 H), 1.35 (m, 1 H), 1.73 (m, 2 H), 2.25 (m, 2 H), 3.16 (d, *J* = 8.7 Hz, 1 H), 3.29 (d, *J* = 8.6 Hz, 1 H), 3.83 (m, 2 H), 4.11 (t, *J* = 7.0 Hz, 2 H), 4.45 (A of AB d, *J* = 12 Hz, 1 H), 4.51 (B of AB d, *J* = 12 Hz, 1 H), 5.71 (m, 1 H), 7.33 (m, 5 H); MS (*m/z*) $[M]^+$ 348, 333, 185, 127, 111, 91, 59, 43.

Epoxy Alcohol 16. To a suspension of powdered 4-Å molecular sieves (3 g) in CH_2Cl_2 at −40 °C was added titanium(IV) isopropoxide (1.1 mL, 3.4 mmol), followed by addition of (−)-diethyl D-tartrate (0.8 mL, 4.2 mmol). After the mixture was stirred for 15 min, a solution of 15 (8 g, 23 mmol) in CH_2Cl_2 (20 mL) was added, and stirring was continued for 30 min prior to addition of *tert*-butyl hydroperoxide (3.8 M solution in toluene, 9.2 mL, 35 mmol). The reaction mixture was warmed to 0 °C over 7 h and then quenched by pouring into a 1-L Erlenmeyer flask containing a mixture of ether (0.3 L) and saturated Na_2SO_4(aq) (9 mL). After mixture was stirred vigorously for 1 h, the precipitated titanium salts were filtered and washed with additional ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (6:1 hexane/ethyl acetate) to give 6.7 g (80%) of 16: $[\alpha]^{24}_D$ −9.43° (*c* 0.53, $CHCl_3$): IR (neat) 3420, 2980, 2860, 1450, 1370, 1220, 1180, 1080, 895, 720, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 0.90 (s, 3 H), 1.30 (s, 6 H), 1.35 (m, 1 H), 1.65 (m, 1 H), 1.83 (m, 2 H), 2.95 (m, 1 H), 3.08 (m, 1 H), 3.16 (d, *J* = 8.6 Hz, 1 H), 3.30 (d, *J* = 8.6 Hz, 1 H), 3.62 (m, 1 H), 3.78–3.95 (m, 3 H), 4.46 (A of AB d, *J* = 12 Hz, 1 H), 4.50 (B of AB d, *J* = 12 Hz, 1 H), 7.32 (m, 5 H); HRMS $[M - CH_3]^+$ calcd 349.2015, found 349.2011.

Diol 17. To a solution of 16 (6.7g, 18.8 mmol) in THF (300 mL) at −40 °C was added dropwise Red-Al (3.4 M solution in toluene, 21.4 mL, 73 mmol). The reaction temperature was maintained at −30 to −20 °C for 72 h, whereupon the reaction was quenched by addition of water (10 mL). Ether (100 mL) was added, and the quenched solution was vigorously stirred for 2 h before the precipitated salts were filtered. The filtrate was concentrated in vacuo to give 5.1 g of crude 17, a pale yellow oil which was used in the next step without further purification. A small sample was purified by SiO_2 chromatography (3:1 hexane/ethyl acetate) for analytical purposes: IR ($CHCl_3$) 3490, 2800, 2760, 1390, 1215, 1085, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 3 H), 0.82 (s, 3 H), 1.22 (s, 3 H), 1.25 (s, 3 H), 1.46 (m, 2 H), 1.62 (m, 7 H), 3.07 (d, *J* = 9.0 Hz, 1 H), 3.22 (d, *J* = 8.0 Hz, 1 H), 3.77 (m, 2 H), 4.05 (m, 2 H), 4.37 (A of AB d, *J* = 12 Hz, 1 H), 4.41 (B of AB d, *J* = 12 Hz, 1 H), 7.26 (m, 5 H).

Silyl Ether 18. To a solution of crude 17 (5.1 g) in DMF (150 mL) at room temperature was added imidazole (2.3 g, 33 mmol) and chlorodiphenyl*tert*-butylsilane (5.9 mL, 23 mmol). After being stirred for 5 h, the reaction mixture was diluted with ether and washed with water and then saturated NaCl(aq). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (10:1 hexane/ethyl acetate) to afford 9.6 g (86%, two steps) of 18: $[\alpha]^{24}_D$ −11.96° (*c* 1.55, $CHCl_3$); IR (neat) 3515, 2980, 2860, 1460, 1440, 1380, 1220, 1090, 730, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 0.89 (s, 3 H), 1.04 (s, 9 H), 1.28 (s, 3 H), 1.32 (s, 3 H), 1.38 (m, 1 H), 1.62–1.75 (m, 5 H), 3.15 (d, *J* = 8.7 Hz, 1 H), 3.30 (d, *J* = 8.6 Hz, 1 H), 3.35 (d, *J* = 3.5 Hz, 1 H), 3.84 (m, 3 H), 4.06 (m, 2 H), 4.43 (A of AB d, *J* = 13 Hz, 1 H), 4.49 (B of AB d, *J* = 13 Hz, 1 H), 7.3–7.4 (m, 11 H), 7.70 (m, 4 H); MS (*m/z*) $[M]^+$ 590, 255, 199, 91.

Methoxymethyl Ether 19. To a solution of 18 (7.2 g, 12 mmol) in diisopropylamine (25 mL) at 0 °C was added portionwise over 1.5 h (bromomethyl)methyl ether (5 mL, 60 mmol). The reaction was allowed to warm to ambient temperature and stirred for 15 h, whereupon CH_2Cl_2 (250 mL) was added. The resultant mixture was then washed with pH 7 phosphate buffer, and the organic layer was removed and dried over $MgSO_4$. After filtration and concentration in vacuo, the residual material (containing the amine) was filtered through SiO_2 (3:1 hexane/ethyl acetate) to yield 10.6 g of crude product. Further purification was accomplished by SiO_2 flash chromatography (30:1 hexane/ethyl acetate)

to give 6.82 g (85%) of **19**: $[\alpha]^{24}_D$ −12.75° (*c* 0.80, $CHCl_3$); IR (neat) 3068, 2960, 2860, 1470, 1430, 1380, 1220, 1100, 1035, 910, 815, 720, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.89 (s, 3 H), 1.04 (s, 9 H), 1.28 (s, 3 H), 1.29 (s, 3 H), 1.30 (m, 2 H), 1.60 (m, 2 H), 1.80 (, 2 H), 3.14 (d, *J* = 8.5 Hz, 1 H), 3.30 (m, 4 H), 3.35 (d, *J* = 6.8 Hz, 1 H), 3.7–3.85 (m, 4 H), 4.45 (m, 2 H), 4.65 (m, 2 H), 7.3–7.45 (m, 11 H), 7.70 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$, decoupled) δ 19.7, 20.6, 24.3, 24.8, 26.9, 33.5, 37.7, 38.5, 42.2, 55.5, 60.4, 63.9, 69.5, 73.2, 73.3, 76.7, 96.7, 100.2, 127.3, 127.6, 128.2, 129.5, 134.0, 135.6; MS (*m/z*) $[M - CH_3]^+$ 633, 255, 199, 91, 45.

Alcohol 20. To a solution of **19** (2.8 g, 4.3 mmol) in absolute ethanol (20 mL) at 25 °C was added freshly neutralized W-2 Raney nickel, prepared by washing 6 mL of a pH 10, 50% slurry of Raney nickel (Aldrich) with 300 mL of water and 250 mL of absolute ethanol. The reaction mixture was heated at 50 °C for 4 h and subsequently filtered. The residual solids were washed with hot methanol, and the combined filtrate was concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (6:1 hexane/ethyl acetate) to give 2.1 g (88%) of **20**: $[\alpha]^{24}_D$ −14.0° (*c* 1.31, $CHCl_3$); IR ($CHCl_3$) 3500, 2937, 2883, 1460, 1423, 1374, 1201 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.86 (s, 3 H), 1.03 (s, 9 H), 1.32 (s, 6 H), 1.42 (m, 1 H), 1.62 (t, *J* = 6.7 Hz, 2 H), 1.79 (m, 3 H), 2.95 (s, 1-O*H*), 3.30 (s, 3 H), 3.35 (dd, *J* = 10, 4.9 Hz, 1 H), 3.54 (dd, *J* = 10, 4.7 Hz, 1 H), 3.72 (m, 3 H), 3.91 (m, 2 H), 4.61 (A of AB d, *J* = 6.6 Hz, 1 H), 4.65 (B of AB d, *J* = 6.6 Hz, 1 H), 7.37 (m, 6 H), 7.66 (m, 4 H).

Aldehyde 21. DMSO (1.1 mL, 14.2 mmol) was added dropwise to a solution of oxalyl chloride (0.7 mL, 8 mmol) in CH_2Cl_2 at −78 °C. After 5 min, a solution of **20** (2.1 g, 3.8 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The reaction was stirred at −78 °C for 1.5 h, whereupon triethylamine (2.5 mL, 18 mmol) was added. The resultant mixture was allowed to warm to 0 °C over 3 h and was subsequently quenched with water (20 mL). The organic layer was separated and washed with additional water and then saturated NaCl(aq). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford crude **21** (2.1 g), which was used in the next step without purification. A small sample was purified by SiO_2 chromatography (10:1 hexane/ethyl acetate) for analytical purposes: $[\alpha]^{24}_D$ −14.80° (*c* 1.28, $CHCl_3$); IR ($CHCl_3$) 2936, 2880, 2860, 1742, 1460, 1421, 1380, 1200, 1090, 815 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.99 (s, 3 H), 1.04 (s, 9 H), 1.30 (s, 6 H), 1.46 (m, 1 H), 1.74 (m, 5 H), 3.30 (s, 3 H), 3.70 (t, *J* = 5.3 Hz, 2 H), 3.91 (m, 3 H), 4.62 (m, 2 H), 7.28 (m, 6 H), 7.66 (m, 4 H), 9.56 (s, 1 H).

Alcohol 22. To a solution of **21** (2.1g, 3.6 mmol) in THF (20 mL) at −78 °C was added MeLi (1.42 M in ether, 3.2 mL, 4.5 mmol) dropwise. After 25 min, the reaction was quenched by pouring into saturated $NaHCO_3$(aq) (15 mL). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (3:1 hexane/ethyl acetate) to give 2.0 g (95%) of **22** as a ca. 2:1 mixture of diasteriomers: IR (neat) 3500, 2880, 1430, 1380, 1210, 1180 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (diastereochemical shift when different is given in brackets) 0.67 [0.82] (s, 3 H), 0.90 [0.88] (s, 3 H), 1.05 (s, 9 H), 1.07 [1.10] (s, 3 H), 1.35 [1.38] (s, 6 H), 1.6–2.0 (m, 7 H), 3.32 (s, 3 H), 3.6–4.0 (m, 6 H), 4.63 (m, 2 H), 7.38 (m, 6 H), 7.66 (m, 4 H).

Ketone 23, Fragment A. DMSO (0.70 mL, 9.9 mmol) was added dropwise to a solution of oxalyl chloride (0.43 mL, 4.9 mmol) in CH_2Cl_2 (25 mL) at −78 °C. After 5 min, a solution of **22** (1.4g, 2.4 mmol) in CH_2Cl (5 mL) was added dropwise. The reaction was stirred at −78 °C for 1.5 h, whereupon triethylamine (1.7 mL, 12 mmol) was added. The resultant mixture was allowed to warm to −30 °C over 4 h and subsequently quenched with water. The organic layer was separated and washed with additional water and then saturated NaCl(aq). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude product. Purification was accomplished by SiO_2 flash chromatography (7:1 hexane/ethyl acetate) to give 1.28 g (92%) of **23**: $[\alpha]^{24}_D$ −60.0° (*c* 0.44, $CHCl_3$); IR (neat) 2936, 1708, 1430, 1382, 1226, 1172, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.04 (s, 3 H), 1.10 (s, 3 H), 1.28 (s, 6 H), 1.43 (m, 2 H), 1.68 (m, 2 H), 1.78 (m, 2 H), 2.15 (s, 3 H), 3.29 (s, 3 H), 3.72 (m, 2 H) 3.87 (m, 2 H), 3.96 (dd, *J* = 9, 7 Hz, 1 H), 4.59 (A of AB d, *J* = 6 Hz, 1 H), 4.63 (B of AB d, *J* = 6 Hz, 1 H), 7.39 (m, 6 H), 7.67 (m, 4 H); HRMS $[M - CH_3]^+$ calcd 555.3138, found 555.3141.

Experimental Procedures for Scheme III: Fragment A via Aldol Methodology. Aldehyde 24. A solution of CH_2Cl_2 (50 mL), *cis*-3-hexen-1-ol (1.0 g, 10 mmol), *N,N*-diisopropylamine (2.7 mL, 15 mmol), catalytic imidazole, and chlorodiphenyl*tert*-butylsilane (2.8 mL, 11 mmol) was stirred at room temperature for 40 h. The reaction mixture was poured into 3:1 hexane/ethyl acetate (200 mL) and washed with saturated $NaHCO_3$(aq) and saturated NaCl(aq). After drying over $MgSO_4$, filtration and concentration in vacuo led to 3.8 g of the crude silyl ether, which was used directly in the next step without purification. A small sample was purified by SiO_2 chromatography (15:1 hexane/ethyl acetate) for analytical purposes: IR (neat) 3100–2720, 1580, 1100–1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 8 Hz, 3 H), 1.02 (s, 9 H), 1.96 (m, 2 H), 2.28 (q, *J* = 7 Hz, 2 H), 3.62 (t, *J* = 8 Hz, 2 H), 5.36 (m, 2 H), 7.37 (m, 6 H), 7.64 (m, 4 H); MS (*m/z*) $[M]^+$ 338, 282, 281.

A stirred solution of this silyl ether (3.8 g, <10 mmol) in 4:1 CH_2Cl_2/MeOH (70 mL) was cooled to −78 °C and subjected to a steady flow of ozone. When the solution remained blue without additional ozone, dimethyl sulfide (3.0 mL, 41 mmol) was added and the cooling bath was removed. After 30 min, triethylamine (3.0 mL, 22 mmol) was added, and the reaction mixture was heated at reflux for 20 min. Phosphate buffer (200 mL, pH 7) was added and the aqueous layer was extracted with 4:1 hexane/ethyl acetate. After drying over $MgSO_4$, filtration, and concentration in vacuo, SiO_2 chromatography (5:1 hexane/ethyl acetate) yielded 2.9 g (87% two steps) of **24**: IR (neat) 3020–2800, 2720, 1740, 1130–1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 2.61 (dt, *J* = 7, 2 Hz, 2 H), 4.02 (t, *J* = 6 Hz, 2 H), 7.40 (m, 6 H), 7.64 (m, 4 H), 9.82 (t, *J* = 3 Hz, 1 H).

Thioester 26. A stirred solution of (*S*)-[3-(3-ethylpentyl)] ethanethioate (87 mg, 0.50 mmol) in pentane (3.0 mL) was cooled to −78 °C. After rapid addition of diisopropylethylamine (107 μL, 0.60 mmol), **2R** (127 μL, 0.60 mmol) was added dropwise. After 30 min the solution was warmed to 0 °C and stirred for 1 h to insure the formation of enolate **25**. Upon cooling to −78 °C, a solution of aldehyde **24** (200 mg, 0.65 mmol) in pentane (0.4 mL) was added dropwise. After 1 h the reaction mixture was warmed to room temperature for 10 min and subsequently quenched by addition of excess *N,N*-dimethylethanolamine. The mixture was diluted with saturated NH_4Cl(aq), extracted with ether, washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (8:1 hexane/ethyl acetate) gave 191 mg of **26** (79%, 89%ee [determined by use of $Eu(hfc)_3$ on the corresponding acetate derivative and corrected for the %ee of the reagent]): IR (neat) 3530–3300, 3000–2810, 1670, 1120–1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7 Hz, 9 H), 1.03 (s, 9 H), 1.77 (m, 2 H), 1.76 (q, *J* = 8 Hz, 6 H), 2.65 (m, 2 H), 3.40 (d, *J* = 4 Hz, 2 H), 3.81 (m, 2 H), 4.28 (m, 1 H), 7.38 (m, 6 H), 7.65 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 429.1919, found 429.1918.

Methoxymethyl Ether 27. A solution of dimethoxymethane (2.2 mL, 24 mmol) and **26** (200 mg, 0.44 mmol) in $CHCl_3$ (3.6 mL) at 0 °C was added to a slurry of P_2O_5 (1 g, 7 mmol) in $CHCl_3$ (3.6 mL) and stirred at 0 °C. After 1.5 h the reaction was complete by TLC and was quenched by addition of saturated Na_2CO_3(aq), extracted with ether, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude oil was purified by preparative TLC (10:1 hexane/ethyl acetate) to obtain 196 mg (91%) of **27**: IR 2980–2810, 1670, 1100–1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7 Hz, 9 H), 1.04 (s, 9 H), 1.77 (q, *J* = 7 Hz, 6 H), 1.78 (m, 2 H), 2.63 (dd, *J* = 14, 7 Hz, 1 H), 2.77 (dd, *J* = 14, 7 Hz, 1 H), 3.27 (s, 3 H), 3.72 (m, 2 H), 4.20 (m, 1 H), 4.59 (A of AB d, *J* = 7 Hz, 1 H), 4.61 (B of AB, *J* = 7 Hz, 1 H), 7.38 (m, 6 H), 7.62 (m, 4 H); MS (*m/z*) $[M]^+$ 530, 473, 472.

Ketone 28. At 0 °C, DMS·CuBr (250 mg, 1.2 mmol) was stirred in ether (5.0 mL), and MeLi (1.7 M in ether, 1.4 mL, 2.4 mmol) was added dropwise. The reaction vessel was cooled to −78 °C, and a solution of **27** (196 mg, 0.37 mmol) was added dropwise in ether (0.5 mL). The reaction mixture was warmed −15 °C and stirred for 1 h. After quenching with saturated NH_4Cl(aq) and extracting with ether, the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Preparative TLC (8:1 hexane/ethyl acetate) led to 145 mg (94%) of **28**: IR

2980–2820, 1710, 1100–1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.85 m, 2 H), 2.12 (s, 3 H), 2.55 (dd, J = 14, 7 Hz, 1 H), 2.74 (dd, J = 14, 7 Hz, 1 H), 3.25 (s, 3 H), 3.72 (m, 2 H), 4.22 (m, 1 H), 4.58 (AB apparent singlet, 2 H), 7.37 (m, 6 H), 7.63 (m, 4 H); HRMS $[M - CH_3]^+$ calcd 399.1992, found 399.1989.

Ketol 30. A solution of **28** (119 mg, 0.29 mmol) in ether (2.5 mL) and pentane (2.5 mL) was stirred at −78 °C. *N,N*-Diisopropylethylamine (0.20 mL, 0.66 mmol) was added rapidly, followed by dropwise addition of **2S** (73 μL, 0.33 mmol) (analogously, **2R** and *meso*-2,5-dimethylborolanyl triflate were used in their respective reactions). After 2 h, a solution of aldehyde **29** (66 mg, 0.35 mmol) was added dropwise in pentane (0.5 mL). After an additional hour the reaction was quenched by addition of excess *N,N*-dimethylethanolamine, warmed to 0 °C, and diluted with saturated NH_4Cl(aq). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organics were washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. After preparative TLC (6:1 hexane/ethyl acetate), 152 mg (87%) of **29** was obtained: IR (neat) 3800–3300, 2990–2840, 1720, 1100–1070 cm^{-1}; ^1H NMR (300 MHz, CDL_3) δ 0.87 (s, 3 H), 0.94 (s, 3 H), 1.07 (s, 9 H), 1.79 (m, 2 H), 2.52 (m, 1 H) 2.60 (dd, J = 15, 6 Hz, 1 H), 2.80 (dd, J = 15, 7 Hz, 1 H), 3.28 (s, 3 H), 3.29 (m, 1 H), 3.42 (d, J = 5 Hz, 1 H), 3.74 (m, 2 H), 4.02 (m, 1 H), 4.30 (m, 1 H), 4.51 (s, 2 H), 4.60 (m, 2 H), 7.33 (m, 5 H), 7.40 (m, 6 H), 7.66 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 549.2672, found 549.2669.

Diol 31. To a solution of **30** (108 mg, 0.18 mmol) in MeCN (1.0 mL) at −78 °C was added a solution of $Me_4NB(OAc)_3H$ (230 mg, 0.90 mmol) in 1:1 MeCN/AcOH (2.0 mL). The reaction was maintained at −20 °C and stirred for 38 h. The mixture was diluted with ether and quenched with solid $NaHCO_3$. The organics were washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (2:1 hexane/ethyl acetate) gave 77 mg of a major product and 16 mg of a minor product (86% combined): ^1H NMR (250 MHz, $CDCl_3$) (where the chemical shift differs in the minor diastereomer it appears in brackets) δ 0.92 [0.84] (s, 3 H), 0.94 [0.90] (s, 3 H), 1.06 [1.07] (s, 9 H), 1.2–1.7 (m, 6 H), 3.36 (m, 2 H), 3.38 [3.32] (s, 3 H), 3.45 [3.50] (OH, 1 H), 3.53 [3.62] (OH, 1 H) 3.76 (m, 2 H), 3.83 (m, 1 H), 4.07 (m, 1 H), 4.18 (m, 1 H), 4.48 (A of AB d, J = 8 Hz, 1 H), 4.51 (B of AB d, J = 8 Hz, 1 H), 4.63 (d, J = 6 Hz, 1 H), 4.69 (d, J = 6 Hz, 1 H), 7.32 (m, 5 H), 7.40 (m, 6 H), 7.67 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 551.2828, found 551.2830.

Fragment A. Intermediate 19 from Diol 31. To a solution of diol **31** (5*R*,7*S*) (72 mg, 0.12 mmol) in CH_2Cl_2 (1.0 mL) was added 2,2-dimethoxypropane (12 μL, 0.10 mmol) and catalytic PPTS (2 mg). After 1.5 h the reaction was complete, and the mixture was diluted with ether. The organics were washed with saturated $CuSO_4$(aq), water, saturated $NaHCO_3$(aq), and saturated NaCl(aq) and dried over $MgSO_4$, filtered, and concentrated in vacuo. Preparative TLC (20:1 hexane/ethyl acetate) led to 72 mg (98%) of **19**, identical with authentic **19** (prepared as illustrated in Scheme II) as indicated by ^1H NMR, ^{13}C NMR, IR, MS, and $[\alpha]^{24}_D$ [cf. −12.64° (*c* 0.72, $CHCl_3$)].

Experimental Procedures for Scheme IV: Fragment B. Alcohol 33 via THP Ether 32. To a solution of 3-butyn-1-ol (3.1 g, 30 mmol) and DHP (2.4 g, 29 mmol) in CH_2Cl_2 (50 mL) was added catalytic PPTS (10 mg). After 3 h the reaction was complete by TLC, and the reaction mixture was diluted with ether and washed with 50% NaCl(aq). The aqueous washes were back-extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Short-path distillation (79–82 °C, 14 mm) afforded 4.8 g (89%) of **32**: IR (neat) 3290–3240, 2940–2820, 2100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45–1.88 (m, 6 H), 1.96 (t, J = 2.3 Hz, 1 H), 2.48 (dt, J = 6.7, 2.3 Hz, 2 H), 3.50 (m, 2 H), 3.82 (m, 2 H), 4.63 (t, J = 3.9 Hz, 1 H).

To a solution of **32** (4.8 g, 31 mmol) in THF (100 mL) at −78 °C was added *n*-BuLi (1.4 M solution in hexanes, 25 mL, 36 mmol) dropwise. After 1 h at −30 °C, gaseous formaldehyde (excess) was bubbled through the solution for 30 min. The reaction mixture was quenched with saturated NH_4Cl(aq) and diluted with ether. The organic layer was separated, washed with saturated NaCl(aq), and concentrated in vacuo. Flash SiO_2 chromatography (2:1 hexane/ethyl acetate) led to 4.9 g (89%) of **33**: IR (neat) 3520–3200, 2920–2810, 2210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.4–2.0 (m, 6 H), 2.50 (tt, J = 7, 3 Hz, 2 H), 3.50 (m, 2 H), 3.82 (m, 2 H), 4.22 (t, J = 2 Hz, 2 H), 4.61 (t, J = 5 Hz, 1 H); HRMS $[M - H]^+$ calcd 183.1021, found 183.1021.

Iodide 34. To ether (600 mL) was added Red-Al (3.4 M in toluene, 77 mL, 272 mmol). To this mechanically stirred solution maintained at 0 °C was added **33** (25 g, 136 mmol) in ether (50 mL), dropwise. After 1 h at room temperature, the reaction mixture was recooled to 0 °C and quenched by addition of ethyl acetate (13 mL, 133 mmol). After the mixture was cooled to −78 °C, iodine (50 g, 197 mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by slow addition of saturated Na_2SO_3(aq), and the organic layer was separated and successively washed with Na_2SO_3(aq), water, and saturated NaCl(aq). The resulting organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash SiO_2 chromatography (2:1 hexane/ethyl acetate) gave 39.5 g (94%) of **34**: IR (neat) 3510–3180, 2980–2820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.4–1.8 (m, 6 H), 2.79 (dt, J = 6, 2 Hz, 2 H), 3.51 (m, 2 H), 3.83 (m, 2 H), 4.20 (t, J = 6 Hz, 2 H), 4.66 (t, J = 2 Hz, 1 H), 5.95 (t, J = 5 Hz, 1 H); MS (*m/z*) $[M]^+$ 312, 185, 85.

Silyl Ether 35. To a solution of **34** (12.0 g, 38.5 mmol) and imidazole (5.54 g, 82.0 mmol) in DMF (150 mL) at 0 °C was added chlorodiphenyl*tert*-butylsilane (10.5 mL, 40.5 mmol). After being stirred for 30 min at 0 °C and 5 min at room temperature, the reaction mixture was quenched with saturated NH_4Cl(aq), extracted with ether, washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 21 g (crude weight) of **35**, which was used in the next step without further purification. A small sample was purified by flash SiO_2 chromatography (12:1 hexane/ethyl acetate) for analytical purposes: IR (neat) 3100–2830, 1160–1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.4–1.8 (m, 6 H), 2.73 (dt, J = 2, 6 Hz, 2 H), 3.49 (m, 2 H), 3.80 (m, 2 H), 4.22 (dd, J = 2, 4 Hz, 2 H), 4.59 (t, J = 4 Hz, 1 H) 5.94 (t, J = 5 Hz, 1 H), 7.38 (m, 6 H), 7.65 (m, 4 H).

Bisolefin 36. To a solution of **35** (21 g, 38 mmol) in THF (100 mL) at −78 °C was added CuI (0.43 g, 2.3 mmol) and then allylmagnesium bromide (1.0 M ether solution, 53 mL, 53 mmol) dropwise. The mixture was allowed to warm to 0 °C over 2 h and was stirred for an additional 2 h, whereupon it was quenched with saturated NH_4Cl(aq). The mixture was extracted with ether and the combined organics were washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash SiO_2 chromatography (12:1 hexane/ethyl acetate) led to 14.6 g (82%, two steps) of **36**: IR (neat) 3080–2780, 1630, 1120–1000, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.4–1.7 (m, 6 H), 2.30 (dt, J = 7, 2 Hz, 2 H), 2.63 (d, J = 7 Hz, 2 H), 3.46 (m, 2 H), 3.83 (m, 2 H), 4.23 (d, J = 6 Hz, 2 H), 4.60 (t, J = 4 Hz, 1 H), 4.92 (m, 2 H), 5.54 (m, 2 H), 7.40 (m, 6 H), 7.68 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 407.2042, found 407.2044.

Alcohol 37. To a solution of **36** (14.6 g, 31.5 mmol) in ethanol (100 mL) was added PPTS (0.95 g, 3.8 mmol), and the mixture was maintained at 50 °C for 2 h. Upon cooling, the reaction mixture was quenched with saturated $NaHCO_3$(aq), and the ethanol was removed in vacuo. The resulting cloudy solution was diluted with ether, and the aqueous layer was removed. The ethereal solution was washed with saturated NaCl(aq), dried over $MgSO_4$, and concentrated in vacuo. Flash SiO_2 chromatography (4:1 hexane/ethyl acetate) led to 11.0 g (92%) of **37**: IR (neat) 3580–3200, 3080–2800, 1630, 1120–1000, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.42 (br s, 1 H), 2.24 (dt, J = 6, 2 Hz, 2 H), 2.61 (d, J = 6 Hz, 2 H), 3.64 (t, J = 6 Hz, 2 H), 4.26 (d, J = 6 Hz, 2 H), 4.93 (m, 2 H), 5.58 (m, 2 H), 7.41 (m, 6 H), 7.68 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 323.1468, found 323.1465.

Aldehyde 38, Fragment B. To a solution of pyridine (6.6 mL, 82 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added CrO_3 (4.1 g, 41 mmol) in one portion. After stirring for 15 min at room temperature, a solution of **37** (2.4 g, 6.3 mmol) in CH_2Cl_2 (10 mL) was rapidly added. The mixture was stirred for 15 min at room temperature, diluted with ether, and washed with 5% NaOH(aq), 5% HCl(aq), water, and saturated $NaHCO_3$(aq). The ethereal solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting 2.4 g of crude **38** (>95% purity by ^1H NMR) was used in the next reaction without further purification (substantial decomposition occurs on SiO_2 chromatography): IR (neat)

3060–2800, 2730–2660, 1710, 1630, 1100–1000 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.03 (s, 9 H), 2.62 (nd, J = 6 Hz, 2 H), 3.01 (d, J = 2 Hz, 2 H), 4.26 (d, J = 6 Hz, 2 H), 4.93 nm, 2 H), 5.56 (m, 2 H), 7.40 (m, 6 H), 7.68 (m, 6 H), 9.54 (t, J = 2 Hz, 1 H).

Experimental Procedures for Scheme V: Completion of the AB Fragment. The AB Coupling: Ketol 39 from 23 (Fragment A) and 38 (Fragment B). To a solution of **23** (500 mg, 0.90 mmol) in ether (15 mL) at −78 °C was added diisopropylethylamine (0.62 mL, 3.6 mmol) followed by the dropwise addition of **2R** (225 mg, 0.90 mmol) (analogously, **1R** and diethylboryl triflate were used in their respective reactions). After stirring for 30 min, a solution of **38** (azeotroped with toluene, 500 mg, 1.3 mmol) in ether (2 mL) was added, and the resultant solution was stirred for an additional 1 h at −78 °C. The reaction was quenched by addition of *N,N*-dimethylethanolamine, warmed to 0 °C, and diluted with saturated NH_4Cl(aq) and ether. The organic layer separated and successively washed with saturated NH_4Cl(aq) and saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash SiO_2 chromatography (4:1 hexane/ethyl acetate) yielded 718 mg (82%) of **39**: IR (neat) 3080–2800, 1695, 1420, 1130–1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 21 H), 1.12 (s, 3 H), 1.28 (s, 6 H), 1.3–1.9 (m, 8 H), 2.15 (m, J = 7 Hz, 2 H), 2.63 (m, 3 H), 3.00 [2.95: minor diastereomer] (d, J = 2 Hz, 1 H) 3.30 (s, 3 H), 3.7–4.0 (m, 6 H), 4.13 (m, 1 H), 4.23 (d, J = 5.9 Hz, 2 H), 4.60 (A of AB d, J = 6.6 Hz, 1 H), 4.63 (B of AB d, J = 6.7 Hz, 1 H), 4.92 (m, 2 H), 5.57 (m, 2 H), 7.39 (m, 12 H), 7.67 (m, 8 H); HRMS [M − OCH_3 − C_4H_9 − H]$^+$ calcd 859.4426, found 859.4422.

Methyl Acetal 40. To a stirring solution of **39** (963 mg, 1.06 mmol) in methanol (16 mL) and methyl orthoformate (2.3 mL) was added PPTS (25 mg, 0.10 mmol). After stirring for 2.5 h at ambient temperature, the mixture was quenched with aqueous $NaHCO_3$, extracted with ether, and washed with water and saturated NaCl(aq). The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Analysis of the crude mixture (^1H NMR) revealed a 6:1 ratio of diastereomers. Flash SiO_2 chromatography (5:1 hexane/ethyl acetate) yielded 143 mg of the minor diastereomer contaminated with **40** and 638 mg of pure **40** (85% combined): IR (neat) 3600–3220, 3040–2810, 2220, 1700, 1140, 1000, 900, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (when data from the minor diastereomer differs, it appears in brackets) δ 0.89 (s, 3 H), 0.98 (s, 3 H), 1.04 (s, 18 H), 1.2–1.9 (m, 6 H), 2.03 (dd, J = 13, 6 Hz, 1 H), 2.28 [2.23] (dd, J = 13, 6 Hz, 1 H), 2.66 [2.67] (m, 1 H), 3.21 [3.20] (s, 3 H), 3.29 [3.30] (s, 3 H), 3.55 (br s, 1 H), 3.75 (t, J = 6.2 Hz, 2 H), 3.83 (m, 1 H), 3.91 (m, 1 H), 4.02 (m, 1 H), 4.17 [4.22] (m, 1 H), 4.22 (d, J = 6 [7] Hz, 2 H), 4.60 (A of AB d, J = 6.4 Hz, 1 H), 4.62 (B of AB, J = 6.2 Hz, 1 H), 4.91 (m, 2 H), 5.57 (m, 2 H), 7.38 (m, 12 H), 7.67 (m, 8 H); MS (m/z) [M − CH_3O − H]$^+$ 891, 877, 874, 873, 872, 835, 834, 833.

Organomercurial Chloride 41. To a solution of **40** (633 mg, 0.69 mmol) in THF (6.9 mL) and methanol (1.7 mL) at room temperature was added portionwise $Hg(OAc)_2$ (264 mg, 0.83 mmol). The colorless solution was stirred for 5 h, whereupon the reaction was quenched by addition of saturated KCl(aq). After the quenched reaction mixture was stirred for 30 min, water (4 mL) was added and the resultant mixture was extracted with ether. The combined organic extract was washed with saturated $NaHCO_3$(aq) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo to afford the crude product, which was immediately acetylated without further purification. The crude organomercurial product was treated with AcCl (0.254 mL, 3.45 mmol) in CH_2Cl_2 (17 mL) and pyridine (0.86 mL) at 0 °C for 2 h. The reaction was quenched by addition of water, and the products were extracted with ether. The combined organic extract was washed with saturated $CuSO_4$(aq), water, and saturated NaCl(aq) and dried over $MgSO_4$. Filtration and concentration in vacuo afforded crude **41**, which was purified by flash SiO_2 chromatography (4:1 hexane/ethyl acetate) to yield 694 mg (84%) of **41** as a white foam: IR (CH_2Cl_2) 3020–2800, 1735, 1700, 1230, 1110–980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 1.04 (s, 21 H), 1.16–2.33 (m, 12 H), 2.03 (s, 3 H), 3.13 + 3.17 (s, 3 H), 3.28 + 3.30 (s, 3 H), 3.30 + 3.54 (m, 1 H), 3.76 (m, 4 H), 3.87 (m, 2 H), 4.18 (m, 3 H), 4.59 + 4.61 (AB apparent singlets, 2 H), 5.19 + 5.22 (m, 1 H), 5.40 + 5.48 (t, J = 7 Hz, 1 H), 7.43 (m, 12 H), 7.68 (m, 8 H); MS (m/z) [M − CH_3O]$^+$ 1168, 1148, 1145, 1141, 1111, 1061.

Alcohol 42. Through a solution of **41** (552 mg, 0.46 mmol) in CH_2Cl_2 (13 mL) was passed a steady stream of O_2 for 10 min from a compressed gas cylinder via a glass capillary tube (solution volume was maintained at >10 mL by replacing evaporated CH_2Cl_2). In a separate vessel, a slurry of $NaBH_4$ (160 mg, 4 mmol) was stirred in DMF (4 mL) and flushed with oxygen in a similar manner for 2–3 min. The borohydride solution was then slowly added to the organomercural chloride solution via cannula over a period of 5 min. Oxygen was passed through the reaction mixture for the next 1–2 h, whereupon the reaction was quenched by addition of saturated NH_4Cl(aq) and extracted with ether. The combined organic extract was washed with water and saturated $NaHCO_3$ and dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, the crude product was purified by flash SiO_2 chromatography (5:1 hexane/ethyl acetate) to give 365 mg (81%) of **42** as a 1:1 mixture of diastereomers: IR (CH_2Cl_2) 3600–3240, 3040–2810, 1740, 1700, 1140, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 + 0.94 (s, 3 H), 1.04 (s, 21 H), 1.2–2.3 (m, 10 H), 2.03 + 2.04 (s, 3 H), 3.14 + 3.18 (s, 3 H), 3.29 (s, 3 H), 3.3–3.6 (m, 2 H), 3.64 + 4.09 (m, 1 H), 3.73 (m, 3 H), 3.90 (m, 1 H), 4.19 (m, 2 H), 4.60 (AB apparent singlet, 2 H), 5.19 (m, 1 H), 5.44 + 5.47 (t, J = 7Hz, 1 H), 7.35–7.42 (m, 12 H), 7.66 (m, 8 H); HRMS [M − CH_3O − CH_3O]$^+$ calcd 916.4766, found 916.4770.

Aldehyde 44, the AB Fragment (via 43, its 1:1 diastereometric mixture). To a solution of oxalyl chloride (32 μL, 0.37 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added DMSO (52 μL, 0.74 mmol). After 5 min, a solution of **42** (180 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After an additional 30 min at −78 °C, triethylamine (136 μL, 0.90 mmol) was added dropwise, and the mixture was warmed to ambient temperature, stirred for 30 min, and diluted with ether. The organic mixture was washed with 10% HCl(aq), water, and saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude **43**, which hydrates readily, was azeotroped with toluene and subjected to epimerization without further purification: ^1H NMR (250 MHz, $CDCl_3$) (chemical shifts for *cis*-**43** is presented with data for *trans*-**43** in brackets when different) δ 0.94 [0.93] (s, 3 H), 1.03 (s, 21 H), 2.04 [2.05] (s, 3 H), 1.62–2.12 (m, 8 H), 2.27 (d, J = 16 Hz, 1 H), 2.43 (d, J = 16 Hz, 1 H), 3.16 (m, 1 H), 3.19 (s, 3 H), 3.28 (s, 3 H), 3.44 (dd, J = 11, 2.7 Hz, 1 H), 3.58 (m, 1 H), 3.75 (t, J = 6.0 Hz, 2 H), 3.91 (m, 1 H), 4.21 (d, J = 6.6 Hz, 2 H), 4.59 (AB apparent singlet, 2 H), 5.19 (dd, J = 16, 5.4 Hz, 1 H), 5.47 [5.43] (t, J = 6.6 Hz, 1 H), 7.62–7.65 (m, 12 H), 7.67 (m, 8 H), 9.53 [9.62] (s, 1 H).

To a solution of dried aldehyde (180 mg, 0.18 mmol) in benzene (9 mL) was added active Al_2O_3 (Woelm B, 3% H_2O [Act. II], 1.8 g). The resulting slurry was stirred for 20 h at ambient temperature, filtered through Celite (washing with CH_2Cl_2 and ether), and concentrated in vacuo to yield 130 mg (74%) of **44** (*cis*-**43**) (9:1 cis/trans by ^1H NMR): ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (s, 3 H), 1.03 (s, 21 H), 2.04 (s, 3 H), 1.62–2.12 (m, 8 H), 2.27 (d, J = 16 Hz, 1 H), 2.43 (d, J = 16 Hz, 1 H), 3.16 (m, 1 H), 3.19 (s, 3 H), 3.28 (s, 3 H), 3.44 (dd, J = 11, 2.7 Hz, 1 H), 3.58 (m, 1 H), 3.75 (t, J = 6.0 Hz, 2 H), 3.91 (m, 1 H), 4.21 (d, J = 6.6 Hz, 2 H), 4.59 (apparent singlet, 2 H), 5.19 (dd, J = 16, 5.4 Hz, 1 H), 5.47 (t, J = 6.6 Hz, 1 H), 7.62–7.65 (m, 12 H), 7.67 (m, 8 H), 9.53 (s, 1 H).

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Supplementary Material Available: ^1H NMR spectra for compounds 3–28, 30–42, and 44 (39 pages). Ordering information is given on any current masthead page.

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TRIPLE ASYMMETRIC SYNTHESIS FOR FRAGMENT ASSEMBLY: VALIDITY OF APPROXIMATE MULTIPLICATIVITY OF THE THREE DIASTEREOFACIAL SELECTIVITIES

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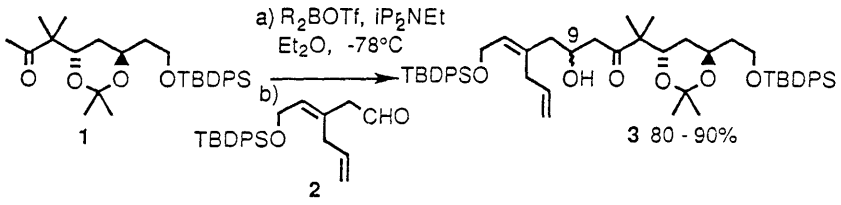
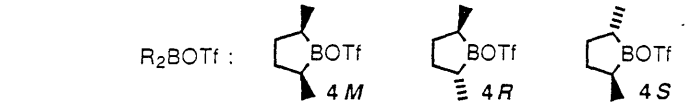
Summary: A strategy of triple asymmetric synthesis is illustrated to be effective for stereochemical control in fragment assembly, a task often encountered in convergent natural product synthesis. The stereochemical outcome of aldol reactions involving three chiral components supports a rule of approximate multiplicativity of facial selectivities intrinsic to the chiral reactants involved in each reaction.

Stereochemical control in the formation of a stereogenic center or centers is most crucial during fragment assembly for a convergent synthesis of a complex natural product. For this process, consider an aldol reaction which involves an achiral aldehyde (constituting one synthetic fragment) and an enolate derived from a chiral ketone (the other fragment). The use of a enantiomerically pure reagent to mediate the ketone enolization and subsequent aldol reaction predictably modifies the diastereofacial selectivity (D.S.) intrinsic to the corresponding enolate prepared from an achiral reagent and thereby results in enrichment of the desired diastereomeric aldol product.[1,2] Selection of a *R*- or *S*- external chiral reagent[3] provides a means of control. This strategy of external chiral reagent control is thus embodied in the precepts of double asymmetric synthesis and has recently been applied in several fragment assemblies[1,4] Such developments suggest the possibility of attaining enhanced stereoselection upon invoking the interaction of a greater number of chiral components which react in concert. This concept has now been subjected to the experimental test and we herein record the first examples of triple asymmetric synthesis involving two chiral fragments and a chiral reagent. Two such examples (see Schemes II and III) utilize fragments made available in connection with ongoing projects aimed at the syntheses of bryostatins[5] and calyculins[6] and serve to uphold the validity of approximate multiplicativity of the diastereofacial selectivities intrinsic to the three chiral components.

The boron mediated aldol reactions involving (achiral) aldehyde **2** and (chiral) ketone **1** (Scheme I) were first examined for the purpose of comparing these reactions with those described below for triple asymmetric synthesis.[7] The reaction mediated by the achiral 2,5-*meso*-dimethylborolanyl trifluoromethanesulfonate[3] (4*M*) established the intrinsic D.S. of ketone **1** as *ca.* 3:1 favoring the 9*S* isomer of **3**. The use of chiral (2*R*,5*R*)-dimethylborolanyltriflate (4*R*) a reagent predicted to be matched with **1**, increased the selectivity to an 8:1 preference.[8] In contrast, (2*S*,5*S*)-dimethylborolanyl triflate (4*S*) mediated a 1:2 preference for formation of the 9*R* stereoisomer thereby constituting a mismatched process.

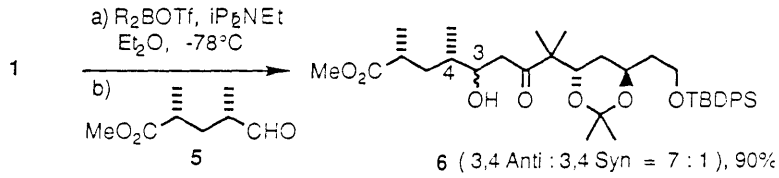
Scheme I





C(9) Stereoselectivity, (*S* : *R*)	3 : 1	8 : 1	1 : 2

Scheme II

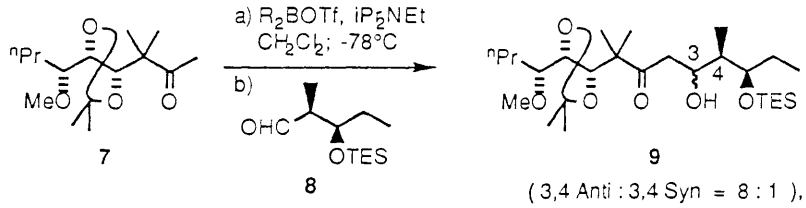


Triple Asymmetric Aldol Results

1 $\xrightarrow[5]{4\,R}$ 6 (3,4 Anti : 3,4 Syn = 25 : 1), 94%

1 $\xrightarrow[5]{4\,S}$ 6 (3,4 Anti : 3,4 Syn = 1 : 1), 92%

Scheme III



Triple Asymmetric Aldol Results

7 $\xrightarrow[8]{4\,R}$ 9 (3,4 Anti : 3,4 Syn = 19 : 1), 84%

$\xrightarrow[8]{4\,S}$ 9 (3,4 Anti : 3,4 Syn = 2 : 1), 81%

Example 1 of Triple Asymmetric Synthesis. Having secured the D.S. of ketone **1**, we chose the well studied (-)-aldehyde **5**[9] of known D.S. (*ca.* 2:1, 3,4-anti selective) to examine triple asymmetric synthesis (Scheme II). As expected for this pair (predicted at *ca.* 3×2), the double asymmetric aldol reaction with the achiral Et_2BOTf provided the aldol products **6** with a 7:1 anti/syn selection. Matched with both **1** and **5** is the chiral reagent 4*R*, and its utilization in the triple asymmetric aldol reaction enhanced the above selection to 25:1, thus exemplifying the stereoselection achieved in a fully matched system.[10] The matched-mismatched reaction using 4*S*, which led to a 1:1 formation of the diastereomers (*ca.* 3×2/3), demonstrates how selection of reagent chirality may be utilized to enhance formation of either diastereomer.[11]

Example 2. As depicted in Scheme III, a reaction between chiral ketone **7**[12] with (+)-aldehyde **8**[13] mediated by Et_2BOTf afforded the aldol products **9** with an 8:1 anti/syn selection. The use of triple asymmetric synthesis in this instance through mediation with the 4*R* reagent enhanced the selectivity to afford a 19:1 anti/syn diastereomeric ratio. Utilization of the 4*S* reagent enabled significant formation of the 3,4-syn diastereomer with an anti/syn ratio of 2:1.[14,15]

The above two examples validate an approximate multiplicativity rule even for triple asymmetric synthesis. High levels of stereocontrol are readily attained for systems consisting of three matched components. The results also indicate that reagents with a larger D.S. than those described above will override any opposing substrate preference in mismatched systems, providing full stereochemical control, simply through the selection of a proper reagent. Triple asymmetric synthesis will prove to be a powerful strategy for fragment assembly with controlled creation of correct stereochemistry.

Acknowledgements. This work was supported by NIH Grant no. GM35879. We thank Dr. J. Cho for kindly supplying a quantity of ketone **7**. M.H.N. and J.C.R. are NIH postdoctoral and predoctoral trainees (NCI T32-CA09112), respectively, and P.S. is a Swedish Natural Science Research Council postdoctoral fellow.

References and Footnotes

1. A subtle but important distinction should be noted between fragment assembly and stereo-selective addition of acetate and propionate equivalents to a chiral aldehyde via the aldol reaction. See: Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* 1989, *54*, 2817.

2. For reviews of double asymmetric synthesis, see: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* 1985, *24*, 1. (b) Sharpless, K. B. *Chimica Scripta* 1985, *25*, 71. (c) Masamune, S.; in *Stereochemistry of Organic and Bioorganic Transformations;* Bartmann, W.; Sharpless, K. B., Ed.; VCH Verlagsgesellschaft mbH, Weinheim, 1987: pp. 49-71.

3. Masamune, S.; Sato, T.; Kim, B.-M.; Wollmann, T. A. *J. Am. Chem. Soc.* 1986, *108*, 8279.

4. (a) Masamune, S. *Pure Appl. Chem.* 1988, *60*, 1587. (b) Paterson, I.; Lister, M. A.; *Tetrahedron Lett.* 1988, *29*, 585. (d) Paterson, I.; McClure, C. K. *Tetrahedron* 1987, 1229.

5. Potent antineoplastic agents, first isolated: Pettit, G. R.; Day, J. F.; Hartwell, J. L.; Wood, H. B. *Nature* (London) 1970, *227*, 962. See also (a) Pettit, G. R.; Herald, C. L.; Doubec, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* 1982, *104*, 6846. (b) Pettit, G. R.; Leet, J. E.; Herald, C. L.; Kamano, Y.; Boettner, F. E.; Baczyncky, L.; Nieman, R. A. *J. Org. Chem.* 1987, *52*, 2854.

6. Antitumor sponge metabolites; see: (a) Kato, Y.; Fusetani, N.; Matsunga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* 1986, *108*, 2780. (b) Kato, Y.; Fusetani, N.; Matsunga, S.; Hashimoto, K.; Fujita, S.; Furuya, T.; Kaseki, K. *Abs. for 28th Natural Prod. Sym., Japan* 1986, 168.

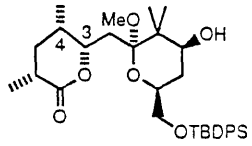
7. The preparation and use of aldehyde **2** was described in an earlier approach to **4** the bryostatins (see Ref. 1). The synthesis of ketone **1** will be reported at a later date as part of a full account on our bryostatin studies.

8. *ca.* 3x3: The D.S. of the borolanyl reagent has been measured at 3-4:1 from reactions of t-butyl methyl ketone with various achiral aldehydes: Kim, B.-M; PhD Thesis, Massachusetts Institute of Technology 1987, pp. 114-131.

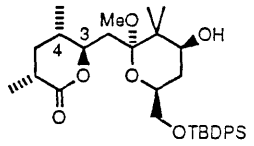
9. Short, R. P.; Masamune, S. *Tetrahedron Lett.* **1987**, *28*, 2841.

10. The aldol reaction of ketone **1** with the (+)-aldehyde **5** as mediated by Et_2BOTf resulted in formation of a 1:1 mixture of diastereomeric aldol adducts, and this pair constituted a mis-matched pair.

11. The 6-syn and 6-anti mixtures were quantitatively converted to the pyranyl lactones **i** and **ii**, respectively, and measurement of the $J_{3,4}$ value in **i** and **ii** confirmed the stereo-selection in the aldol process.



I ($J_{3,4}$ = 3 Hz, ax.-eq.)

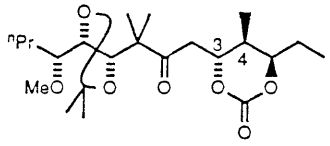


Ii ($J_{3,4}$ = 10 Hz, ax.-ax.)

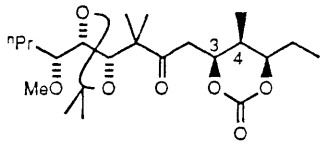
12. The synthesis of ketone **7** will appear at a later date in relation to studies on the total synthesis of calyculin A.

13. (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *Ibid.* **1981**, *103*, 1568.

14. The 9-anti and 9-syn products were converted to the corresponding cyclic carbonates **iii** and **iv**, respectively. Assignment of absolute configuration was accomplished by comparison of the $J_{3,4}$ value in **iii** and **iv**.



III ($J_{3,4}$ = 4 Hz, eq.-eq.)



Iv ($J_{3,4}$ = 2 Hz, ax.-eq.)

15. Experimental and characterization data for compound **1**, **3**, **6-9**, and **i-iv** are available from S.M. upon request.

(Received in USA 14 August 1989)

Synthesis of Bryostatin 7

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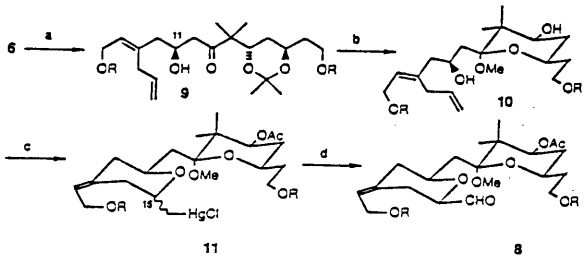
We record herein the synthesis of bryostatin 7 (**1**), a representative member of potent antileukemic agents isolated from the invertebrate filter feeder *Bugula neritina*.[1,2] As previously documented,[3] our earlier efforts toward this objective reached seco-acid derivative **2** corresponding to **1** through the connection of fragments A (**3**), B (**4**), and C (**5**). Unfortunately, deprotection of the C(3)-OMOM group (of **2**), which had been introduced at an early stage and had served well by surviving throughout the course of the synthesis of **2**, turned out to be problematic.[4] This led to a revision of the synthetic route that placed the creation of the C(3) stereogenic center at the end of the seco-acid synthesis. Thus, sequential connection of fragment A′ (**6**) [C(3)–C(10)] [instead of A (**3**) [C(1)–C(10)]], B (**4**), C (**5**), and a C(1)–C(2) unit (**7**) in this order, followed by macrolactonization, completed the synthesis of **1**. All of these fragments were available in our earlier work.[3]

Synthesis of the A′B Fragment (8). The aldol reaction of **4** with the enolate derived from **6** and (*R,R*)-2,5-dimethylborolanyl triflate proceeded with a stereoselection of 8:1 to provide the desired diastereomer **9** as the major product (Scheme I). The two chiral components, **6** and the triflate, constitute a matched pair.[5] With all the carbons in place, **9** was further modified to fragment A′B (**8**). Construction of the two pyran rings was accomplished by deacetonization (step b) to secure **10** followed by Hg-mediated cyclization (step c). The stereorandomness of the latter process as shown in **11** was not critical as this pyran side chain was equilibrated to become equatorial at the aldehyde stage (see **8** and step d, reaction iii) in the manner already detailed for the synthesis of fragment AB.[3b]

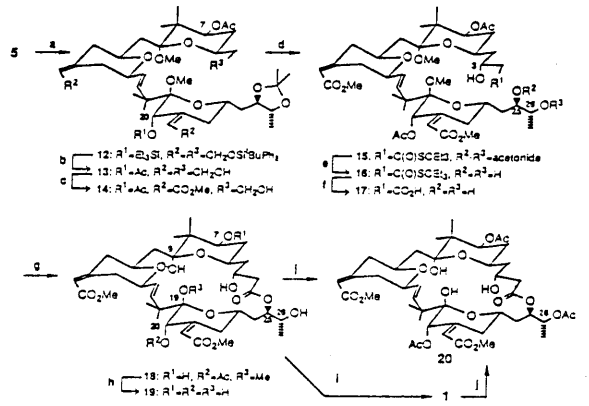
Connection of Fragment A′B, C, and the C(1)–C(2) Unit. The synthesis of fragment C (**5**) has been described elsewhere,[3a] and the characterization of its precursors and an updated synthetic route are provided in the supplementary material. The stereostructure assigned to **5** was confirmed by X-ray analysis of its C(20) hydroxyl compound generated from **5**.[6]

Scheme I[a]



[a] R = Si^{t}BuPh$_2$. (a) (*R,R*)-2,5-Dimethylborolanyl triflate, ^{i}Pr$_2$EtN, Et$_2$O, then **4** (86%, 11*S*:11*R* = 8:1); (b) MeOH, PPTS, (MeO)$_3$CH (84%); (c) (i) Hg(OAc)$_2$, THF–MeOH, then KCl, (ii) Ac$_2$O, pyridine, DMAP (93%, two steps, 15*S*:15*R* = 1:1); (d) (i) NaBH$_4$, O$_2$, DMF–CH$_2$Cl$_2$ (77%), (ii) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, then Et$_3$N, −78 °C, (iii) Al$_2$O$_3$ (3% H$_2$O), CH$_2$Cl$_2$ (60%, two steps).

Scheme II[a]



[a] (a) (i) PhLi, THF, −78 °C, then **8**, then PhCOCl and DMAP, −78 °C → 25 °C, (ii) Na–Hg, MeOH–EtOAc, Na$_2$HPO$_4$, −20 °C (60%, two steps); (b) (i) ^{n}Bu$_4$NF, THF, (ii) ^{t}BuMe$_2$SiCl, DMF, imidazole, (iii) Ac$_2$O, pyridine, DMAP, (iv) ^{n}Bu$_4$NF, THF (100%, four steps); (c) MnO$_2$, THF, then MeOH, NaCN, and AcOH (61%); (d) (i) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, then Et$_3$N, −78 °C → 0 °C, (ii) **7**, ^{i}Pr$_2$EtN, Et$_2$O, −100 °C → −78 °C (83%, two steps, 3*R*:3*S* = 3:1); (e) CSA, MeOH (40%); (f) (i) Et$_3$SiOTf, CH$_2$Cl$_2$, lutidine, 0 °C, (ii) Hg(O$_2$CCF$_3$)$_2$, Na$_2$HPO$_4$, THF, (iii) HF-pyridine, THF, −20 °C (64%, three steps); (g) DCC, PPTS, pyridine, ClCH$_2$CH$_2$Cl, reflux (51%); (h) K$_2$CO$_3$, MeOH, then 5% HCl aqueous workup (54%); (i) (i) ^{t}BuMe$_2$SiCl, DMF, Et$_3$N, DMAP, (ii) Ac$_2$O, pyridine, (iii) HF–MeCN (40%, two steps); (j) Ac$_2$O, pyridine.

(1) (a) Pettit, G. T.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846. (b) Pettit, G. R.; Leet, J. E.; Herald, C. L.; Kamano, Y.; Boettner, F. E.; Baczynskyj, L.; Nieman, R. A. *J. Org. Chem.* **1987**, *52*, 2854 and references cited therein.

(2) For the physiological activity of bryostatins, see: Wender, P. A.; Cribbs, C. M.; Koehler, K. F.; Sharkey, N. A.; Herald, C. L.; Kamano, Y.; Pettit, G. R.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7197.

(3) (a) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587. (b) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, *54*, 2817. (c) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357.

(4) Model experiments carried out prior to our selection of MOM for the C(3) hydroxyl group protection showed that a β-OMOM *carboxylic acid* could be removed under mild acidic conditions, e.g., acetic acid, under which **2** underwent extensive side reactions.

(5) For a double asymmetric synthesis, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(6) We thank Dr. O. Yamashita and Mr. J. Okada for carrying out this analysis, which is detailed in the supplementary material.

Optimization of the Julia–Lythgoe procedure[7] used to couple the two fragments **5** and **8** required extensive experimentation (Scheme II). Phenyllithium was found to be the base of choice for deprotonation of **5** selectively at C(17). The use of weaker bases, e.g., LDA and Et_2NLi, and stronger bases, e.g., *tert*- and *n*-butyllithium, resulted in insufficient deprotonation and concomitant formation of arylic anions,[8] respectively. The presence of Na_2HPO_4 in the reductive elimination (the second reaction of step a) served to retain the C(7) acetate in product **12**.[9] After selective acetylation at C(20), affording triol **13** (step b), and conversion of this bis allylic alcohol to the corresponding bis ester (**14**) (step c), the remaining C(3) hydroxyl group was oxidized and the product aldehyde was treated with chiral enolate reagent **7** (step d, reaction ii) to provide as the major product the 3-hydroxy (instead of MOM-protected 3-hydroxy) seco-acid thiol ester **15**. The two reactants, the aldehyde derived from **14** and enolate **7**, constitute a mismatched pair,[5] and in this context, the stereoselectivity of 3:1 observed in this aldol reaction should be appreciated.

Macrolactonization and Functional Group Manipulation. Thiol ester **15** was sensitive toward acid, but selective removal of its acetonide was achieved with the retention of the methyl acetal functionalities to provide **16** as one diastereomer. This compound was the seco-acid derivative originally designed for macrolactonization at the risk that there are three sites [the C(3), C(25), and C(26) hydroxyl groups] available for lactonization. Since all attempts at the direct lactonization of **16** with a thiophilic metal cation[10] failed, **16** was converted to carboxylic acid **17** with temporary protection of the three hydroxyl groups.[11] It was only after numerous experiments that **17** was macrolactonized in a yield of 51% with a combination of DCC (10 equiv), pyridine (100 equiv), and PPTS (10 equiv).[12,13] Spectral inspection of the product **18** indicated that the lactonization site was indeed C(25)[14] and that the C(9) methyl acetal and C(7) acetate were hydrolyzed under the reaction conditions. After macrolactonization there still remained a problem: the C(19) methoxy group[15] resisted acid hydrolysis probably because of the presence of the electron-withdrawing C(20) acetate group in addition to the excessive steric congestion around the C(19) center. Surprisingly, removal of the acetate followed by acidification solved the problem to give **19**.[16] The triacetate **20** derived from **19** was found to be identical with the acetate of **1**[17] isolated from the natural source to establish the correctness of the stereostructures assigned to all the synthetic intermediates. Selective silation of the C(26) hydroxyl group of **19** followed by acetylation and desilation completed the synthesis of **1** and confirmed as identical the two samples of synthetic and natural origin.[18,19]

Supplementary Material Available: Spectral data for all new compounds, detailed experimental procedures for selected reactions, and details of an X-ray analysis of **5** (24 pages). Ordering information is given on any current masthead page.

(7) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763.
(8) Gais, H.-J.; Ball, W. A.; Bund, J. *Tetrahedron Lett.* **1988**, *29*, 781.
(9) For instance, see: Greck, C.; Grice, P.; Jones, A. B.; Ley, S. V. *Tetrahedron Lett.* **1987**, *28*, 5759.
(10) (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. (c) Park, P.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *Ibid.* **1987**, *109*, 6205.
(11) For the reaction of β-hydroxy carboxylic acid thiol esters, see: (a) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874. (b) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *Ibid.* **1982**, *104*, 5523.
(12) Haslam, E. *Tetrahedron* **1980**, *36*, 2409. Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394. Use of DMAP instead of pyridine gave an intractable mixture.
(13) Model studies were carried out with 3,16-dihydroxyhexadecanoic acid.
(14) An unidentified product isolated in minute quantities could possibly be the C(1)–C(26) lactone. The preference of the C(25) over C(26) was anticipated from molecular models of the seco acid.
(15) In the construction of the C fragment, this methyl acetal was prepared under forcing anhydrous conditions: MeOTMS, TMSOTf (Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357), or $(MeO)_3CH$, BF_3-OEt_2. Therefore this resistance to hydrolysis was anticipated.
(16) For a similar observation, see, inter alia: Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 7530.
(17) Pettit, G. R.; Herald, C. L.; Kamano, Y.; Gust, D.; Aoyagi, R. *J. Nat. Prod.* **1983**, *46*, 528.
(18) NMR spectra (C_6D_6) of bryostatins and their derivatives are often concentration-dependent probably due to the expected intermolecular hydrogen bonding, and each comparison must be made under identical conditions. See also ref 1b.

(19) We thank Professors G. R. Pettit and Y. Kamano for their generous supply of samples of bryostatin 1 and 7 and helpful suggestions, Dr. K. Furihata of Professor H. Seto's laboratory for the measurement of 500-MHz ^1H NMR spectra of advanced intermediates and final products, and the National Institutes of Health for financial support (CA 48175) of the work carried out at MIT. J.C.R. is an NIH predoctoral trainee (NCI T32-CA 09112).

Biographical Note

John was born to Peter and Brenda Roberts on November 22, 1963, in West Lafayette, Indiana (several hours before President John F. Kennedy was assassinated). In 1967, he moved with his parents and his older brother David, to Newton, Massachusetts where Peter and Brenda still reside.

In ninth grade (1977), John met Carla Mattos, a Brazilian student whose mother was doing post doctoral work at MIT. After many trips between Sao Paulo and Newton, Carla and John both attended Clark University, beginning in 1981 and in 1983, they were married.

After graduating from Clark in 1985, John and Carla moved to Cambridge where they both attended MIT. On September 25, 1986, Alexandre de Mattos Roberts was born and on July 7, 1988, Daniel de Mattos Roberts was born. John and Carla's third child is due in April. The Mattos-Roberts family plans to settle in the Boston area.